10/603437

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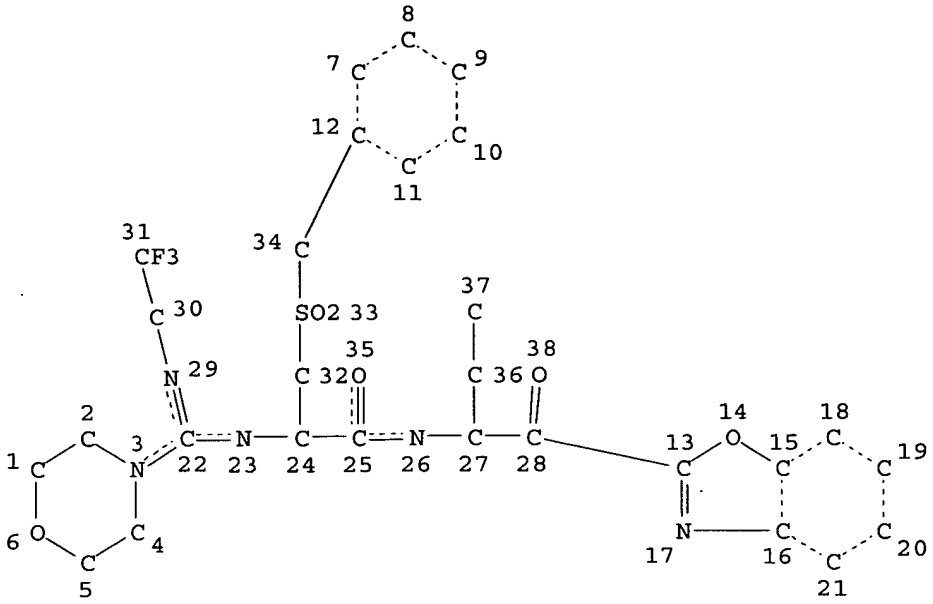


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 38

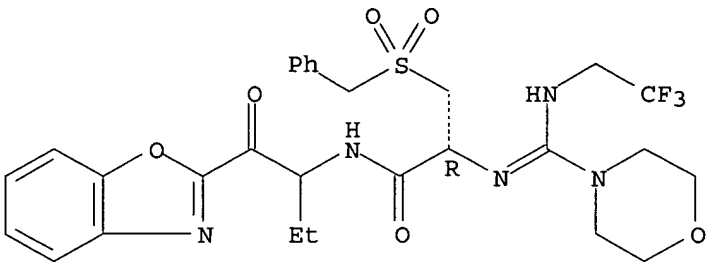
STEREO ATTRIBUTES: NONE
L3 1 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 75 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 639520-24-4 REGISTRY
ED Entered STN: 20 Jan 2004
CN Propanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-2-[[4-morpholinyl[(2,2,2-trifluoroethyl)amino]methylene]amino]-3-[(phenylmethyl)sulfonyl]-, (2R)-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H32 F3 N5 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:77407

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	166.84	167.05

FILE 'CAPLUS' ENTERED AT 12:13:46 ON 24 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 24 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 23 Aug 2005 (20050823/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L4 1 L3

=> d ibib abs hitstr

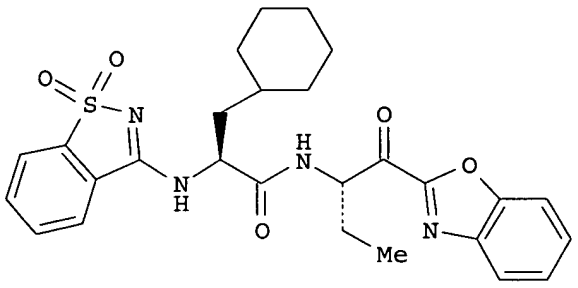
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:2881 CAPLUS
DOCUMENT NUMBER: 140:77407
TITLE: Preparation of peptidic compounds as cysteine protease inhibitors

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

INVENTOR(S): Graupe, Michael; Link, John O.
PATENT ASSIGNEE(S): Axys Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004000838	A1	20031231	WO 2003-US19990		20030624
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004127426	A1	20040701	US 2003-603437		20030624
PRIORITY APPLN. INFO.:			US 2002-391051P	P	20020624
			US 2002-422234P	P	20021030
			US 2002-422710P	P	20021030

OTHER SOURCE(S): MARPAT 140:77407
GI



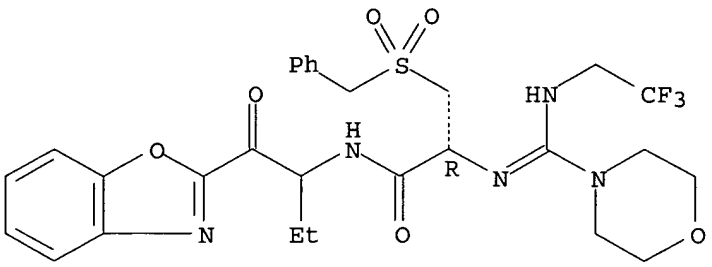
I

AB The invention is directed to compds. R4N:CR3NR2CR1R1aCONH-E and R4R4aNCR3:NCR1R1aCONH-E [E is (functionalized) alkyl or 2-oxo-, 2-thioxo-, or 2-imino(oxa-, thia-, or aza)heterocyclyl; CR1R1a is (un)substituted (hetero)cycloalkylene; R2 is H, OH, alkyl; R3 is H, alkyl, alkoxy, aryloxy, cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, alkyl-, cycloalkyl-, or arylsulfonylalkyl, heterocyclyl, etc.; R4 is H, OH, nitrile, (un)substituted (hetero)alkyl or R3 and R4 form a ring; R4a is (un)substituted (hetero)alkyl] and their pharmaceutically-acceptable salts that are inhibitors of cysteine proteases, in particular cathepsins B, K, L, F, and S, and are therefore useful in treating diseases mediated by these proteases. Thus, peptide I was prepared by condensation of L-cyclohexylalanine hydrochloride with 3-chlorobenzo[d]isothiazole 1,1-dioxide, followed by amidation with (2S)-2-amino-1-benzoxazol-2-ylbutan-1-ol and oxidation with Dess-Martin periodinane.

IT **639520-24-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(preparation of peptidic compds. as cysteine protease inhibitors)
RN 639520-24-4 CAPLUS
CN Propanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-2-[[4-morpholinyl[(2,2,2-trifluoroethyl)amino]methylene]amino]-3-[(phenylmethyl)sulfonyl]-, (2R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil caol;s l3

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.39	172.44

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-0.73

FILE 'CAOLD' ENTERED AT 12:14:03 ON 24 AUG 2005
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

L5 0 L3

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

FULL ESTIMATED COST 0.43 172.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE ENTRY TOTAL SESSION
CA SUBSCRIBER PRICE 0.00 -0.73

FILE 'REGISTRY' ENTERED AT 12:14:06 ON 24 AUG 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 AUG 2005 HIGHEST RN 861509-89-9
DICTIONARY FILE UPDATES: 23 AUG 2005 HIGHEST RN 861509-89-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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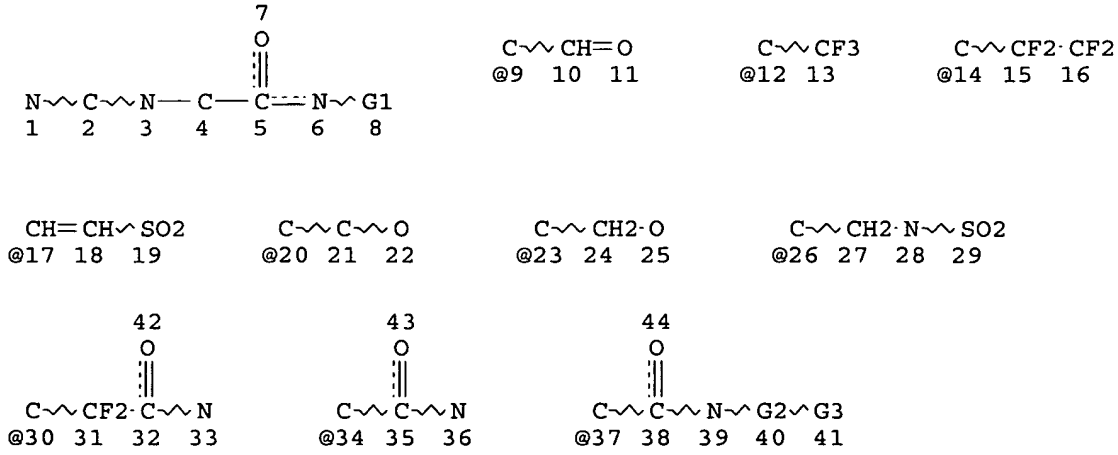
L6 STR



Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

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REP G2=(2-2) CH2
VAR G3=O/N
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE
L8 7608 SEA FILE=REGISTRY SSS FUL L6

100.0% PROCESSED 25318 ITERATIONS 7608 ANSWERS
SEARCH TIME: 00.00.02

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	166.49	339.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.73

FILE 'MEDLINE' ENTERED AT 12:22:08 ON 24 AUG 2005

FILE 'BIOSIS' ENTERED AT 12:22:08 ON 24 AUG 2005
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FILE 'EMBASE' ENTERED AT 12:22:08 ON 24 AUG 2005
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FILE 'CAPLUS' ENTERED AT 12:22:08 ON 24 AUG 2005
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L9 220 FILE MEDLINE
L10 487 FILE BIOSIS
L11 619 FILE EMBASE
L12 1838 FILE CAPLUS

TOTAL FOR ALL FILES
L13 3164 L8

=> s l13 and (cysteine protease or protease inhibit?)
L14 138 FILE MEDLINE
L15 202 FILE BIOSIS
L16 237 FILE EMBASE
L17 405 FILE CAPLUS

TOTAL FOR ALL FILES
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L19           1 FILE MEDLINE
L20           3 FILE BIOSIS
L21          11 FILE EMBASE
L22          20 FILE CAPLUS

TOTAL FOR ALL FILES
L23          35 L13 AND (CYSTEINE PROTEASE INHIBIT?)

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PROCESSING COMPLETED FOR L23
L24          29 DUP REM L23 (6 DUPLICATES REMOVED)

=> d 1-29 ibib abs hitstr;s graupe m?/au and l13

L24  ANSWER 1 OF 29  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:612282  CAPLUS
DOCUMENT NUMBER:          143:133095
TITLE:                    Preparation of amidino derivatives as cysteine
                          protease inhibitors
INVENTOR(S):              Graupe, Michael; Lau, Agnes J.; Li, Jiayao; Link, John
                          O.; Mossman, Craig J.; Woo, Soon H.; Zipfel, Sheila M.
PATENT ASSIGNEE(S):       Axys Pharmaceuticals, Inc., USA
SOURCE:                   PCT Int. Appl., 47 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2005063742         A2    20050714    WO 2004-US43451         20041222
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
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PRIORITY APPLN. INFO.:                    US 2003-532243P     P  20031223
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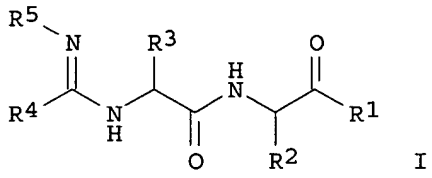

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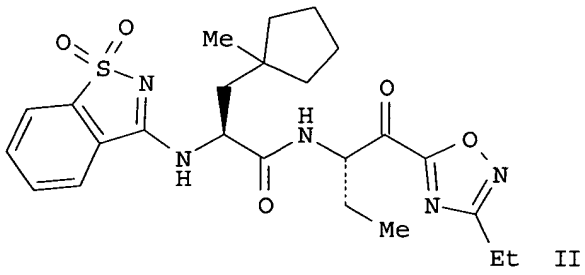


II

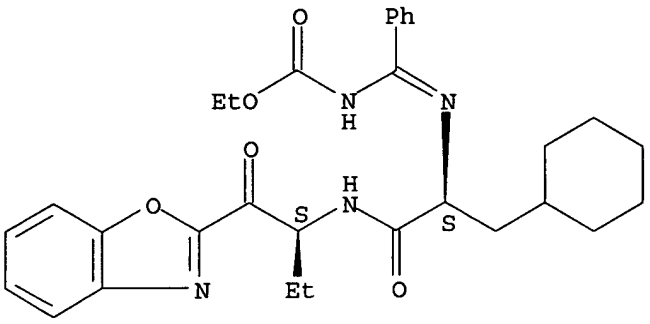
AB Title compds. I [R1 = benzoxazol-2-yl, oxazolo-[4.5-b]-pyridin-2-yl, 2-ethyl-[1.3.4]-oxadizol-5-yl, etc.; R2 = Et, n-propyl; R3 = cyclohexylmethyl, cyclopentylmethyl, 1-methylcyclohexylmethyl, etc.; R4 = Me, Ph, isopropylamine, etc.; R5 = methylsulfonyl, ethoxycarbonyl, pyridin-3-ylsulfonyl, etc.; or R4 and R5 together = 1,1-dioxobenzo[d]isothiazol-3-yl or 1,1-dioxo-1,4-dihydro-λ6-benzo[1.2.4]thiadiazin-3-yl] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of cysteine proteases. Thus, e.g., II was prepared by subsequent couplings of 2(S)-amino-3-cyclopentyl-3-methylpropionic acid hydrobromide with 3-chlorobenzo[d]isothiazole-1,1-dioxide and 2(S)-amino-(3-ethyl-[1.2.4]-oxadiazol-5-yl)butan-1-ol followed by oxidation with Dess-Martin periodinane. The activity of I was evaluated using chromogenic enzyme assays following the inhibition spectrophotometrically (at λ = 460 nm) and it was revealed that compds. of the invention displayed inhibitory activity against cathepsin K, L, S and F (no data). I as inhibitor of cysteine proteases should prove useful in the treatment of psoriasis and Grave's exophthalmos. Pharmaceutical compns. comprising I are disclosed.

IT **858102-01-9P 858102-02-0P 858102-16-6P**
858102-17-7P 858102-18-8P 858102-20-2P
858102-23-5P 858102-24-6P 858102-27-9P
858102-29-1P 858102-33-7P 858102-36-0P
858102-40-6P 858102-41-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amidino derivs. as inhibitors of cysteine proteases)

RN 858102-01-9 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 858102-02-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

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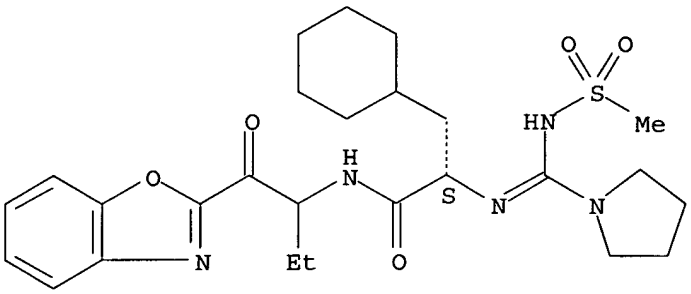
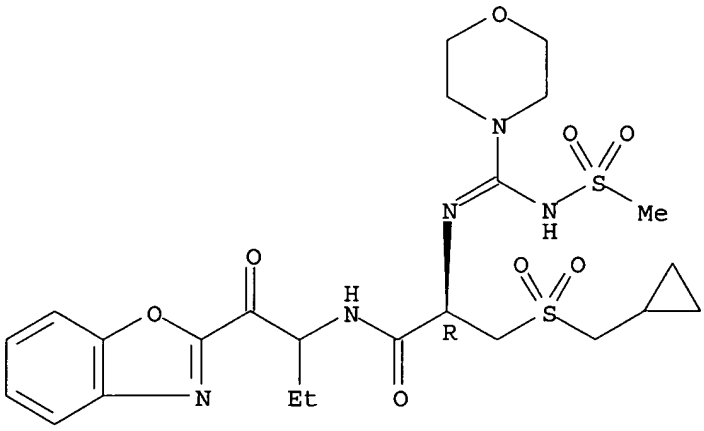


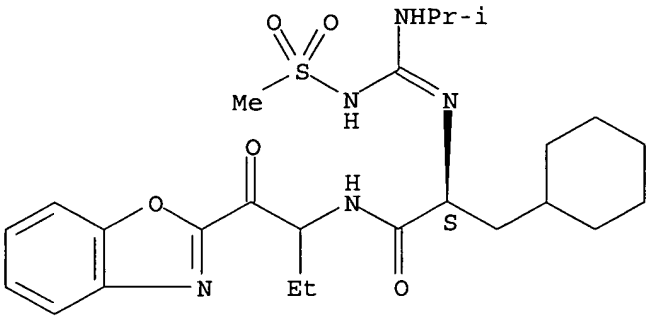
RN 858102-16-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



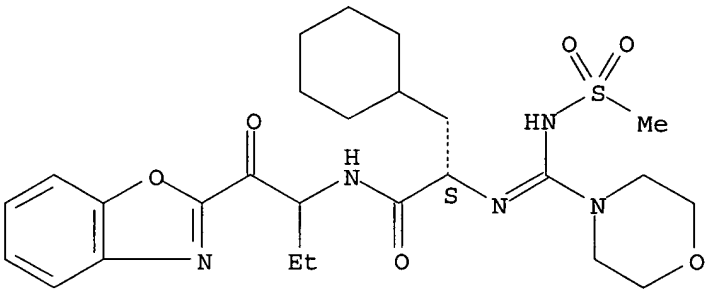
RN 858102-17-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



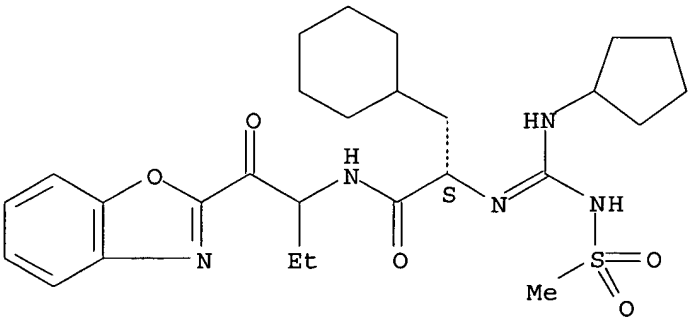
RN 858102-18-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



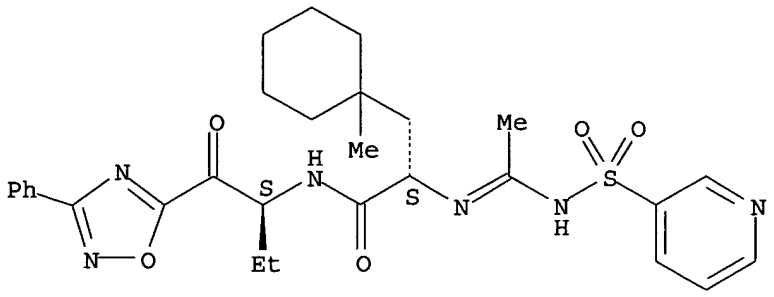
RN 858102-20-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



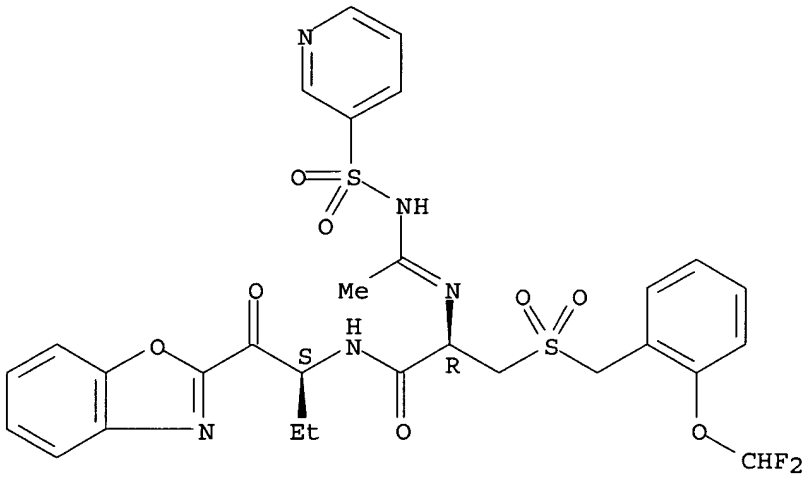
RN 858102-23-5 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



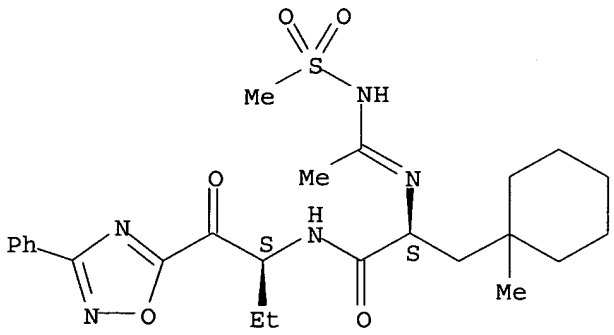
RN 858102-24-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 858102-27-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

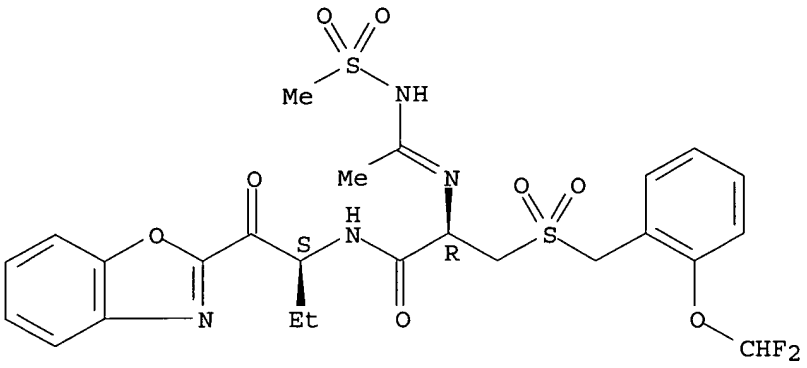
Absolute stereochemistry.



RN 858102-29-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

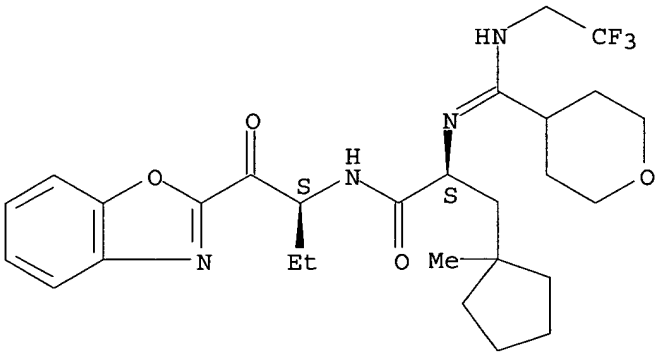
Absolute stereochemistry.

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86



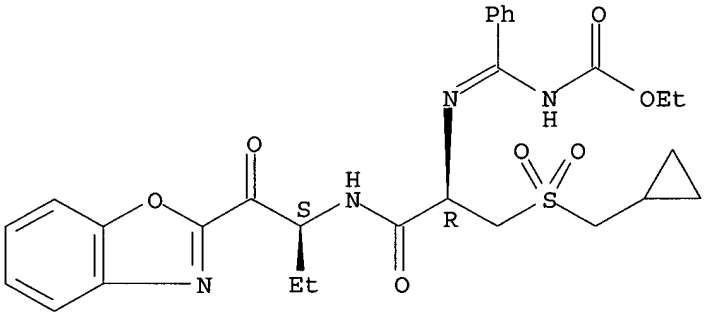
RN 858102-33-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 858102-36-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

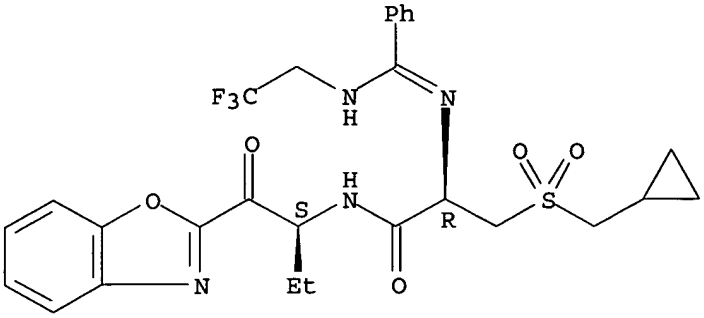
Absolute stereochemistry.



RN 858102-40-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

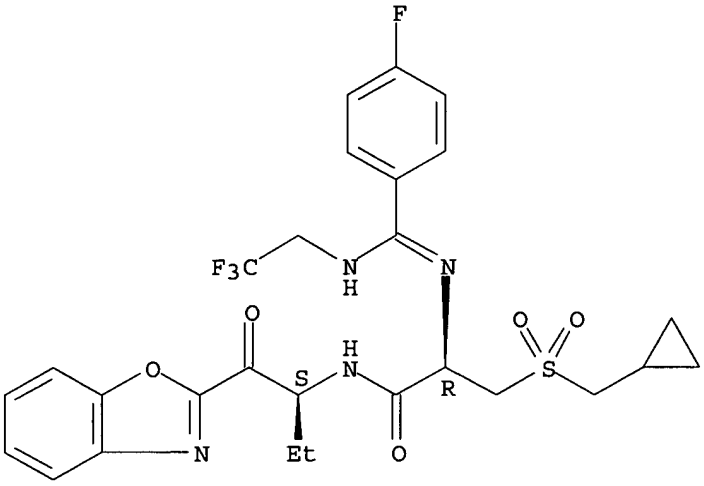
Absolute stereochemistry.

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86



RN 858102-41-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



L24 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1074184 CAPLUS
DOCUMENT NUMBER: 142:56668
TITLE: Preparation of amidino compounds as **cysteine protease inhibitors**
INVENTOR(S): Patterson, John W.
PATENT ASSIGNEE(S): Axys Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004108661	A1	20041216	WO 2004-US17654	20040604

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-475612P P 20030604
OTHER SOURCE(S): MARPAT 142:56668

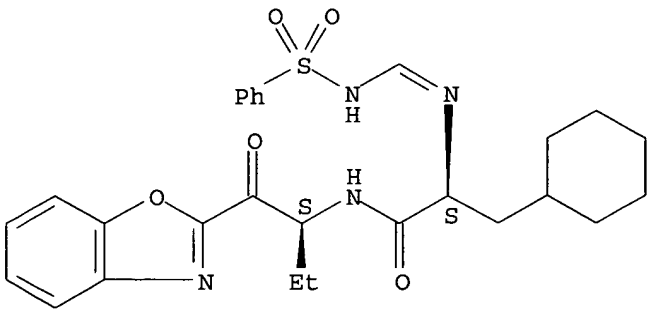
AB The invention is directed to compds. and pharmaceutical compns. that are inhibitors of cysteine proteases, in particular cathepsins B, K, L, F, and S, and are therefore useful in treating diseases mediated by these proteases. Amidines of formulas R4N:CR3NR2CR1R1aCONH-E and R4R4aNCR3:NCR1R1aCONH-E [E is -C(R5)(R6)X1 or -C(R5a)(R6a)CN, where X1 is CHO, -C(R7)(R8)CF3, -C(R7)(R8)CF2CF2R9, -C(R7)(R8)R10, -CH:CHSO2R10, etc.; R5 and R5a are independently H or alkyl; R6 and R6a are independently H, alkyl, haloalkyl, carboxyalkyl, alkoxycarbonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,heteroaryl, etc.; C(R5)(R6) or C(R5a)(R6a) may form rings; R7 is H or alkyl; R8 is OH; or R7 and R8 form oxo; R9 is H, halo, alkyl, aralkyl or heteroaralkyl; R10 is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, or heterocyclylalkyl in which the aromatic or alicyclic ring is optionally substituted; R1, R2 are H or alkyl; R1a is H, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, etc.; or CR1R1a is (un)substituted (hetero)cycloalkylene; R3 is H, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, amino, etc.; R4 is (un)substituted phenyl- or naphthylsulfonyl; R4a is H, alkyl, halo, haloalkyl, hydroxyalkyl, alkoxy,hydroxy, aryl, etc.] or their pharmaceutically-acceptable salts are claimed. Thus, N-[(phenylsulfonylimino)methyl]cyclohexylalanine cyanomethylamide was prepared via reactions of cyclohexylalanine Me ester hydrochloride, Et benzenesulfonylformimidate, and aminoacetonitrile hydrochloride. The biol. examples describe cathepsin assays and pharmaceutical formulations containing compds. of the invention.

IT **808754-86-1P 808754-87-2P 808754-88-3P**
808754-89-4P 808754-90-7P 808754-91-8P
808754-92-9P 808754-93-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amidino compds. as **cysteine protease inhibitors**)

RN 808754-86-1 CAPLUS

CN Cyclohexanepropanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-α-[[[(phenylsulfonyl)amino]methylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

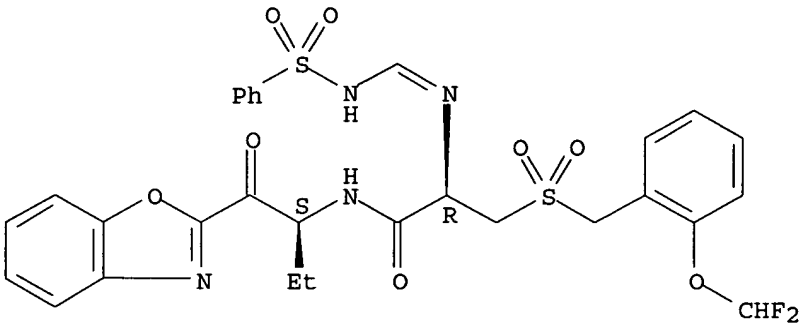
Absolute stereochemistry.



Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

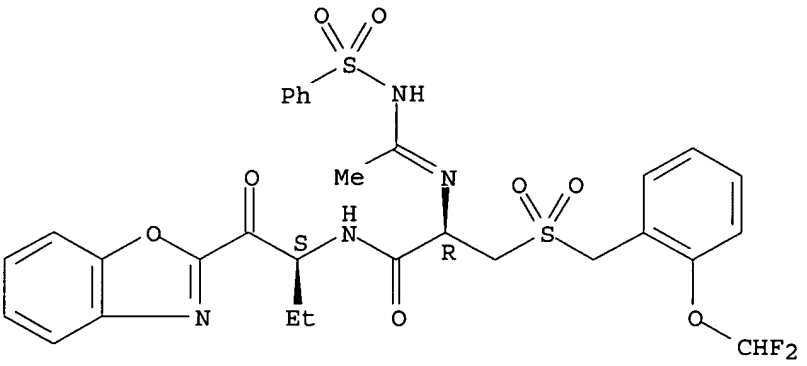
RN 808754-87-2 CAPLUS
CN Propanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-3-[[[2-(difluoromethoxy)phenyl]methyl]sulfonyl]-2-[[[(phenylsulfonyl)amino]methylene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



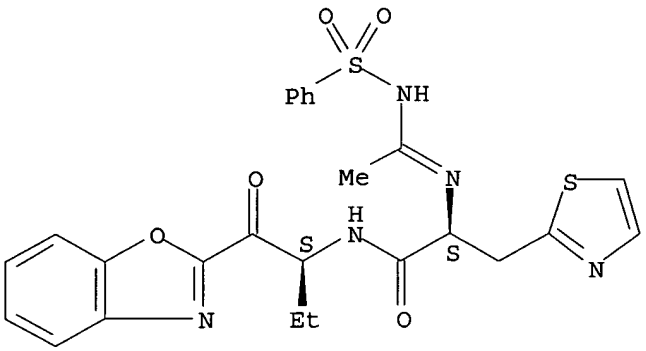
RN 808754-88-3 CAPLUS
CN Propanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-3-[[[2-(difluoromethoxy)phenyl]methyl]sulfonyl]-2-[[1-[(phenylsulfonyl)amino]ethylidene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



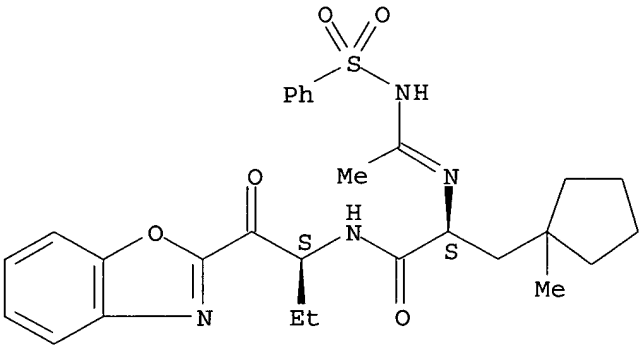
RN 808754-89-4 CAPLUS
CN 2-Thiazolepropanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-α-[[1-[(phenylsulfonyl)amino]ethylidene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



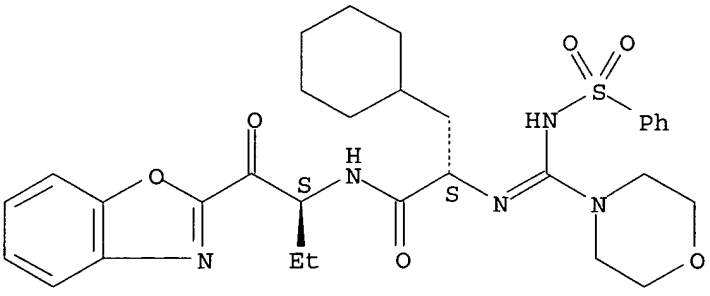
RN 808754-90-7 CAPLUS
CN Cyclopentanepropanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-1-methyl-α-[[1-[(phenylsulfonyl)amino]ethylidene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



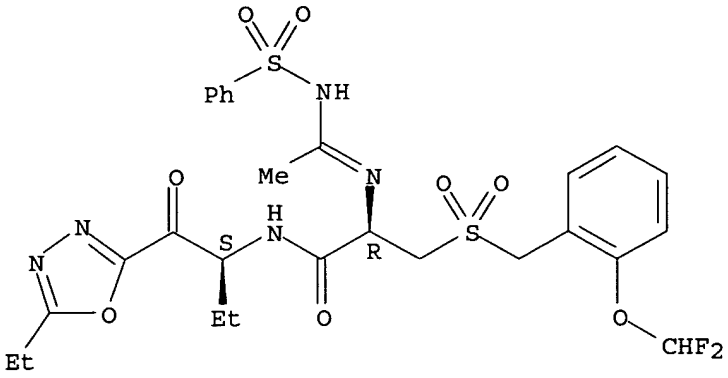
RN 808754-91-8 CAPLUS
CN Cyclohexanepropanamide, N-[(1S)-1-(2-benzoxazolylcarbonyl)propyl]-α-[[4-morpholinyl[(phenylsulfonyl)amino]methylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



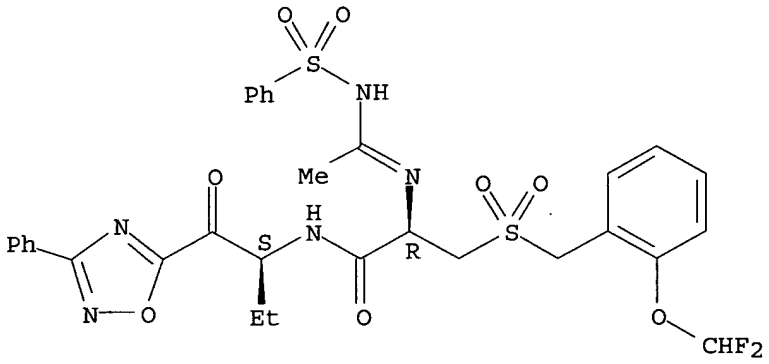
RN 808754-92-9 CAPLUS
CN Propanamide, 3-[[[2-(difluoromethoxy)phenyl]methyl]sulfonyl]-N-[(1S)-1-[(5-ethyl-1,3,4-oxadiazol-2-yl)carbonyl]propyl]-2-[[1-[(phenylsulfonyl)amino]ethylidene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



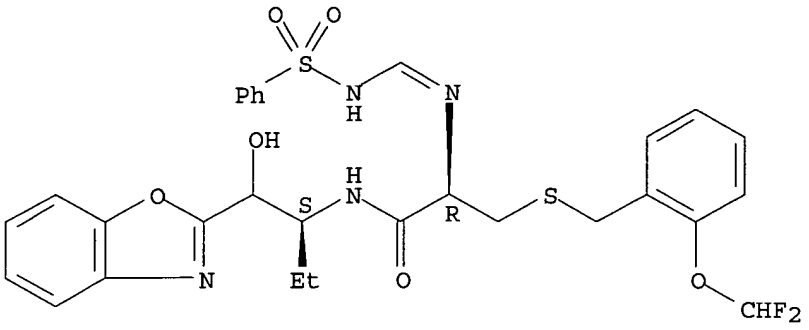
RN 808754-93-0 CAPLUS
CN Propanamide, 3-[[[2-(difluoromethoxy)phenyl]methyl]sulfonyl]-N-[(1S)-1-[(3-phenyl-1,2,4-oxadiazol-5-yl)carbonyl]propyl]-2-[[1-[(phenylsulfonyl)amino]ethylidene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



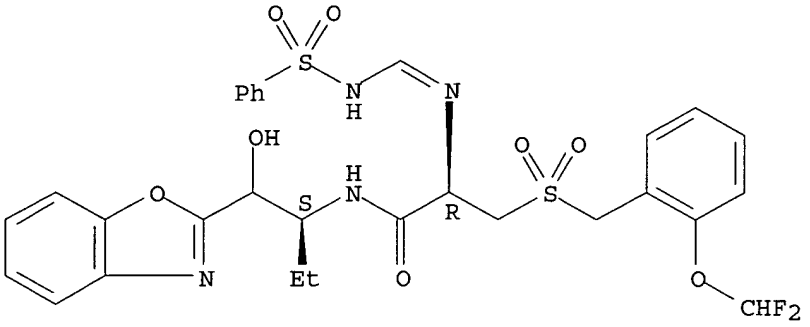
IT **808755-30-8P 808755-32-0P 808755-37-5P 808755-39-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amidino compds. as **cysteine protease inhibitors**)
RN 808755-30-8 CAPLUS
CN Propanamide, N-[(1S)-1-(2-benzoxazolylhydroxymethyl)propyl]-3-[[[2-(difluoromethoxy)phenyl]methyl]thio]-2-[[[(phenylsulfonyl)amino]methylene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



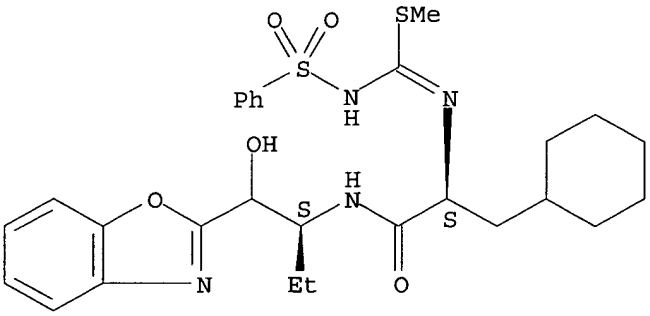
RN 808755-32-0 CAPLUS
CN Propanamide, N-[(1S)-1-(2-benzoxazolylhydroxymethyl)propyl]-3-[[[2-(difluoromethoxy)phenyl]methyl]sulfonyl]-2-[[[(phenylsulfonyl)amino]methylene]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



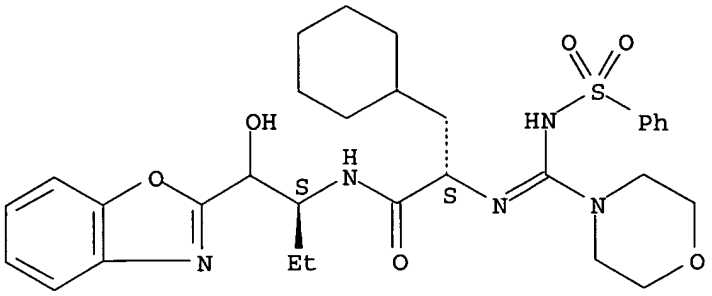
RN 808755-37-5 CAPLUS
CN Carbamimidothioic acid, N-[(1S)-2-[[(1S)-1-(2-benzoxazolylhydroxymethyl)propyl]amino]-1-(cyclohexylmethyl)-2-oxoethyl]-N'-(phenylsulfonyl)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 808755-39-7 CAPLUS
CN Cyclohexanepropanamide, N-[(1S)-1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[4-morpholinyl[(phenylsulfonyl)amino]methylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:872717 CAPLUS
DOCUMENT NUMBER: 141:360716
TITLE: Pharmaco-gene therapy of epithelial sodium channel-associated disorders, and screening methods
INVENTOR(S): Engelhardt, John F.; Zhang, Liang
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004089423	A2	20041021	WO 2004-US9950		20040331
WO 2004089423	A3	20050421			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
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US 2005037497	A1	20050217	US 2004-815262		20040331
US 2005095225	A1	20050505	US 2004-815557		20040331
PRIORITY APPLN. INFO.:			US 2003-459323P	P	20030331
			US 2003-512347P	P	20031016

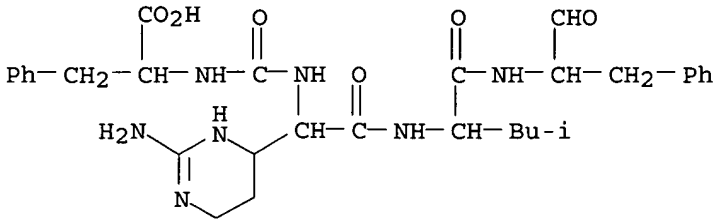
AB The invention discloses agents and methods to alter epithelial sodium channel activity. Also disclosed are e.g. methods for the identification of agents with dual therapeutic activity.

IT **51759-76-3**, Chymostatin A
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaco-gene therapy of epithelial sodium channel-associated disorders, and screening methods)

RN 51759-76-3 CAPLUS

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

CN L-Leucinamide, (2S)-2-[(4S)-2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl]-N-[[[(1S)-1-carboxy-2-phenylethyl]amino]carbonyl]glycyl-N-(1-formyl-2-phenylethyl)- (9CI) (CA INDEX NAME)



L24 ANSWER 4 OF 29 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004244564 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15143461
TITLE: Involvement of secreted Aspergillus fumigatus proteases in disruption of the actin fiber cytoskeleton and loss of focal adhesion sites in infected A549 lung pneumocytes.
AUTHOR: Kogan Tanya V; Jadoun Jeries; Mittelman Leonid; Hirschberg Koret; Osherov Nir
CORPORATE SOURCE: Department of Human Microbiology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
SOURCE: Journal of infectious diseases, (2004 Jun 1) 189 (11) 1965-73. Electronic Publication: 2004-05-11.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20040515
Last Updated on STN: 20040723
Entered Medline: 20040722

AB Aspergillus fumigatus is an opportunistic pathogenic fungus that predominantly infects the respiratory system. Penetration of the lung alveolar epithelium is a key step in the infectious process. The cytoskeleton of alveolar epithelial cells forms the cellular basis for the formation of a physical barrier between the cells and their surroundings. This study focused on the distinct effects of A. fumigatus on the actin cytoskeleton of A549 lung pneumocytes. Of the 3 major classes of cytoskeletal fibers--actin microfilaments, microtubules, and intermediate filaments--only the actin cytoskeleton was found to undergo major structural changes in response to infection, including loss of actin stress fibers, formation of actin aggregates, disruption of focal adhesion sites, and cell blebbing. These changes could be specifically blocked in wild-type strains of A. fumigatus by the addition of antipain, a serine and **cysteine protease inhibitor**, and were not induced by an alkaline serine protease-deficient strain of A. fumigatus. Antipain also reduced, by approximately 50%, fungal-induced A549 cell detachment from the plates and reduction in viability. Our findings suggest that A. fumigatus breaches the alveolar epithelial cell barrier by secreting proteases that act together to disorganize the actin cytoskeleton and destroy cell attachment to the substrate by disrupting focal adhesions.

L24 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:2881 CAPLUS
DOCUMENT NUMBER: 140:77407
TITLE: Preparation of peptidic compounds as **cysteine protease inhibitors**
INVENTOR(S): Graupe, Michael; Link, John O.
PATENT ASSIGNEE(S): Axys Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000838	A1	20031231	WO 2003-US19990	20030624
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004127426	A1	20040701	US 2003-603437	20030624
PRIORITY APPLN. INFO.:			US 2002-391051P P	20020624
			US 2002-422234P P	20021030
			US 2002-422710P P	20021030

OTHER SOURCE(S): MARPAT 140:77407
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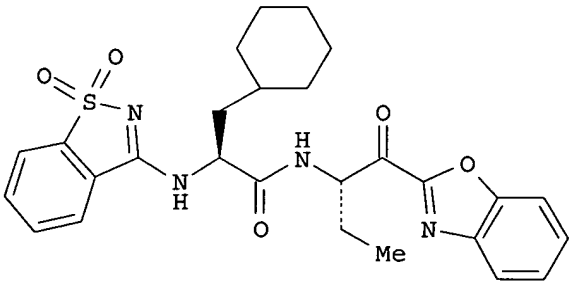


I

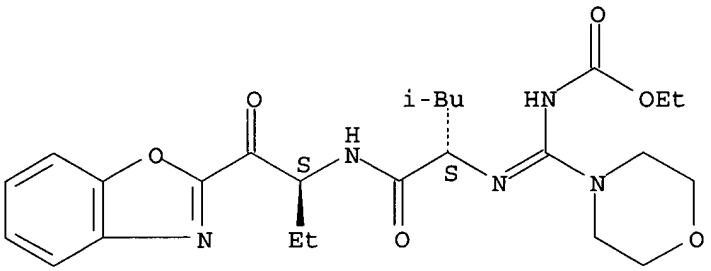
AB The invention is directed to compds. R4N:CR3NR2CR1R1aCONH-E and R4R4aNCR3:NCR1R1aCONH-E [E is (functionalized) alkyl or 2-oxo-, 2-thioxo-, or 2-imino(oxa-, thia-, or aza)heterocyclyl; CR1R1a is (un)substituted (hetero)cycloalkylene; R2 is H, OH, alkyl; R3 is H, alkyl, alkoxy, aryloxy, cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, alkyl-, cycloalkyl-, or arylsulfonylalkyl, heterocyclyl, etc.; R4 is H, OH, nitrile, (un)substituted (hetero)alkyl or R3 and R4 form a ring; R4a is (un)substituted (hetero)alkyl] and their pharmaceutically-acceptable salts that are inhibitors of cysteine proteases, in particular cathepsins B, K, L, F, and S, and are therefore useful in treating diseases mediated by these proteases. Thus, peptide I was prepared by condensation of

L-cyclohexylalanine hydrochloride with 3-chlorobenzo[d]isothiazole 1,1-dioxide, followed by amidation with (2S)-2-amino-1-benzoxazol-2-ylbutan-1-ol and oxidation with Dess-Martin periodinane.

IT **639520-20-0P 639520-21-1P 639520-24-4P 639520-30-2P 639520-34-6P 639520-35-7P 639520-38-0P 639520-39-1P 640276-93-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidic compds. as **cysteine protease inhibitors**)

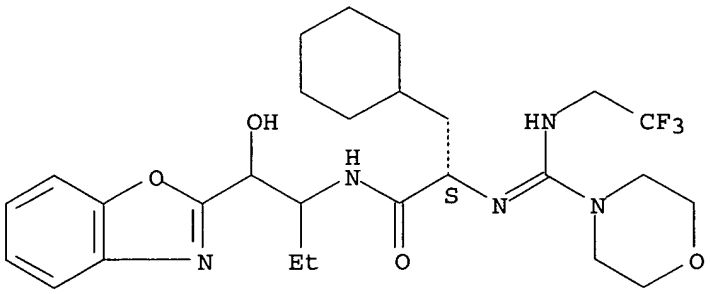
RN 639520-20-0 CAPLUS
CN Carbamic acid, [[[(1S)-1-[[[(1S)-1-(2-benzoxazolylcarbonyl)propyl]amino]carbonyl]-3-methylbutyl]amino]-4-morpholinylmethylene]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



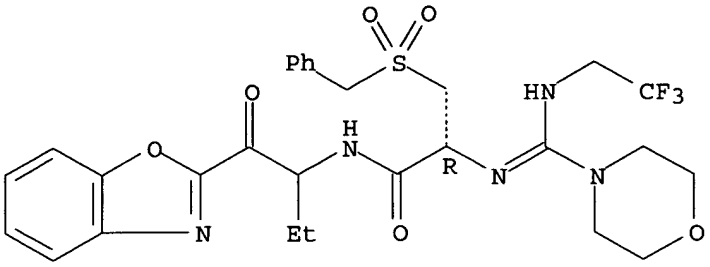
RN 639520-21-1 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[4-morpholinyl[(2,2,2-trifluoroethyl)amino]methylene]amino]-, (αS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



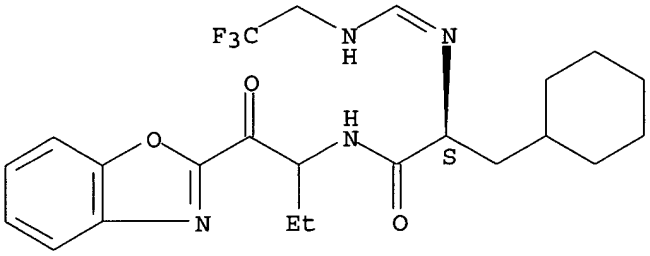
RN 639520-24-4 CAPLUS
CN Propanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-2-[[4-morpholinyl[(2,2,2-trifluoroethyl)amino]methylene]amino]-3-[(phenylmethyl)sulfonyl]-, (2R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



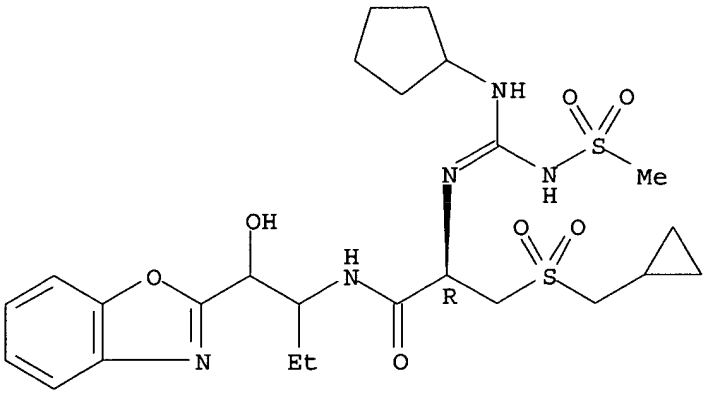
RN 639520-30-2 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-α-[[[(2,2,2-trifluoroethyl)amino]methylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



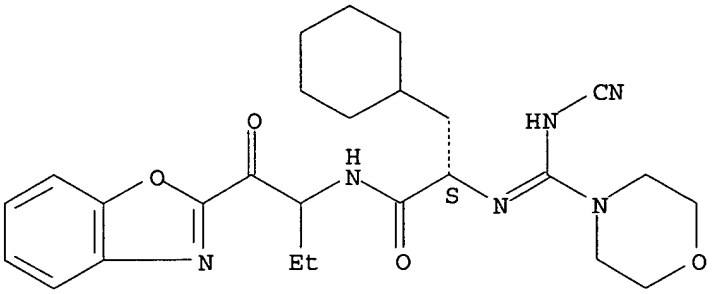
RN 639520-34-6 CAPLUS
CN Propanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-2-[[(cyclopentylamino)[(methylsulfonyl)amino]methylene]amino]-3-[(cyclopropylmethyl)sulfonyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



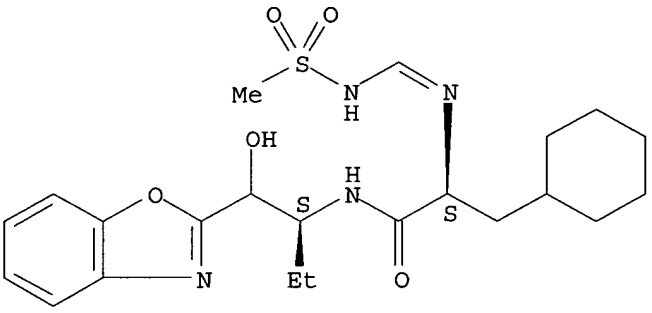
RN 639520-35-7 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-α-[[(cyanoamino)-4-morpholinylmethylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



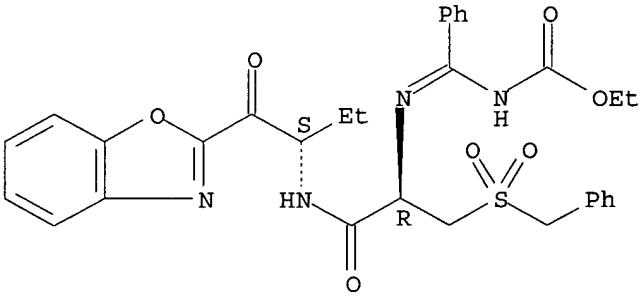
RN 639520-38-0 CAPLUS
CN Cyclohexanepropanamide, N-[(1S)-1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[[(methylsulfonyl)amino]methylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

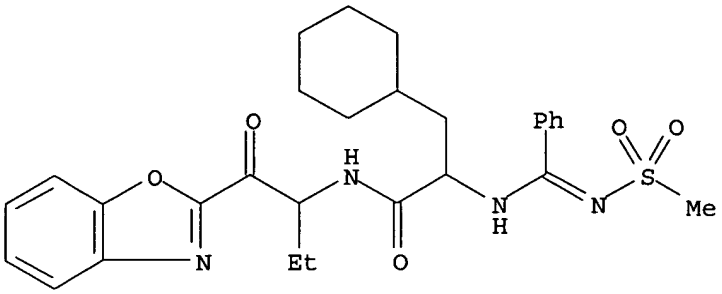


RN 639520-39-1 CAPLUS
CN Carbamic acid, [[[(1R)-2-[[(1S)-1-(2-benzoxazolylcarbonyl)propyl]amino]-2-oxo-1-[[(phenylmethyl)sulfonyl]methyl]ethyl]amino]phenylmethylene]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



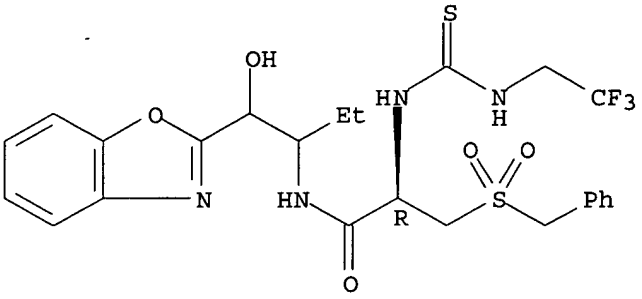
RN 640276-93-3 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylcarbonyl)propyl]-α-[[(E)-[(methylsulfonyl)imino]phenylmethyl]amino]-, (αS)- (9CI) (CA INDEX NAME)



IT **639520-22-2P 639520-23-3P 639520-32-4P**
639520-41-5P 639520-45-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidic compds. as **cysteine protease inhibitors**)

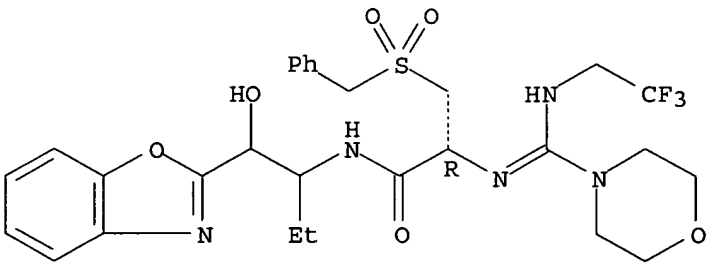
RN 639520-22-2 CAPLUS
CN Propanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-3-[(phenylmethyl)sulfonyl]-2-[[thioxo[(2,2,2-trifluoroethyl)amino]methyl]amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 639520-23-3 CAPLUS
CN Propanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-2-[[4-morpholinyl[(2,2,2-trifluoroethyl)amino]methylene]amino]-3-[(phenylmethyl)sulfonyl]-, (2R)- (9CI) (CA INDEX NAME)

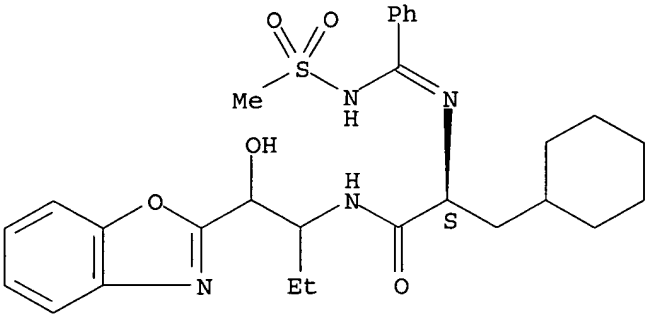
Absolute stereochemistry.



RN 639520-32-4 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[[(methylsulfonyl)amino]phenylmethylene]amino]-, (αS)- (9CI) (CA

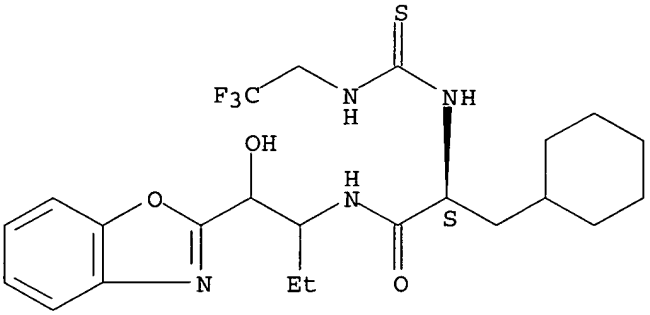
INDEX NAME)

Absolute stereochemistry.



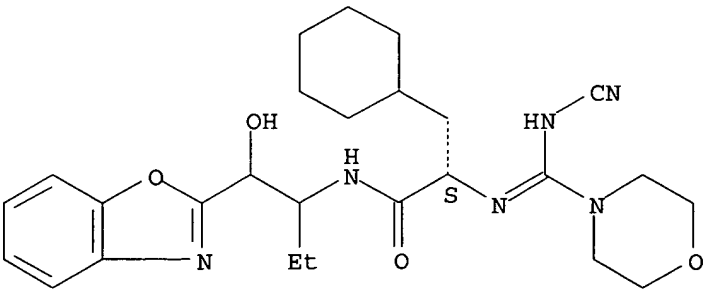
RN 639520-41-5 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[thioxo[(2,2,2-trifluoroethyl)amino]methyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 639520-45-9 CAPLUS
CN Cyclohexanepropanamide, N-[1-(2-benzoxazolylhydroxymethyl)propyl]-α-[[(cyanoamino)-4-morpholinylmethylene]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

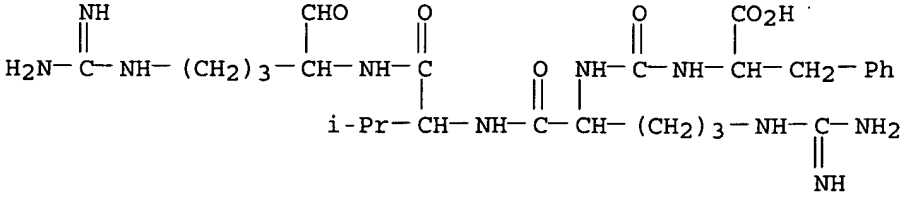
ACCESSION NUMBER: 2003:319745 CAPLUS
DOCUMENT NUMBER: 138:314594
TITLE: Drugs ameliorating hypo-hdl cholesterolemia
INVENTOR(S): Yokoyama, Shinji; Arakawa, Reijiro
PATENT ASSIGNEE(S): Grelan Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033023	A1	20030424	WO 2002-JP10620	20021011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2463395	AA	20030424	CA 2002-2463395	20021011
EP 1435244	A1	20040707	EP 2002-785923	20021011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005085408	A1	20050421	US 2003-492482	20021011
PRIORITY APPLN. INFO.:			JP 2001-314756 A	20011012
			WO 2002-JP10620 W	20021011

AB It is intended to provide drugs ameliorating hypo-HDL cholesterolemia, preventives/remedies for arteriosclerosis, and a method of preventing/treating these diseases/symptoms targeting HDL without needing any genetic engineering techniques. Namely, clin. useful drugs ameliorating hypo-HDL cholesterolemia and preventives/remedies for arteriosclerosis which contain a **cysteine protease inhibitor** as the active ingredient and thus can enhance the expression dose of ABCA1 and increase HDL in the blood without employing any genetic engineering techniques.

IT **37691-11-5**, Antipain
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cysteine protease inhibitors** from microorganisms, plants, and animals for ameliorating hypo-hdl cholesterolemia and as antiatherosclerotics)

RN 37691-11-5 CAPLUS
CN L-Valinamide, N2-[[(1-carboxy-2-phenylethyl)amino]carbonyl]-L-arginyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 2
ACCESSION NUMBER: 2003:299981 BIOSIS
DOCUMENT NUMBER: PREV200300299981
TITLE: Possible identity of IL-8 converting enzyme in human fibroblasts as a cysteine protease.
AUTHOR(S): Ohashi, Kensaku [Reprint Author]; Sano, Emiko; Nakaki, Toshio; Naruto, Masanobu
CORPORATE SOURCE: Toray Medical Co., Ltd., 2-1, Kinshi 1-chome, Sumida-ku, Arca Central 21F, Tokyo, 130-0013, Japan
Kensaku_Ohashi@tmc.toray.co.jp
SOURCE: International Immunopharmacology, (April 2003) Vol. 3, No. 4, pp. 609-614. print.
ISSN: 1567-5769 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 1 Aug 2003

AB A converting activity was characterized in human diploid fibroblasts, which secrete 72IL-8 and 77IL-8 in treatment with IFN-beta and poly I: poly C. 77IL-8 was significantly converted to 72IL-8 by a partially purified fraction of the culture supernatant of human diploid fibroblasts. The converting activity, which was temperature-dependent and optimal at pH 6, was completely inhibited by **cysteine protease inhibitors**, antipain dihydrochloride and E-64, but not by other types ofprotease inhibitors. These data clearly show that human diploid fibroblasts are capable of processing IL-8 to produce a mature IL-8 and that the putative converting enzyme appears to be a cysteine protease.

L24 ANSWER 8 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:26931 CAPLUS
DOCUMENT NUMBER: 138:317374
TITLE: Structure-activity relationships for inhibition of cysteine protease activity and development of Plasmodium falciparum by peptidyl vinyl sulfones
AUTHOR(S): Shenai, Bhaskar R.; Lee, Belinda J.; Alvarez-Hernandez, Alejandro; Chong, Pek Y.; Emal, Cory D.; Neitz, R. Jeffrey; Roush, William R.; Rosenthal, Philip J.
CORPORATE SOURCE: Department of Medicine, San Francisco General Hospital, University of California, San Francisco, CA, 94143-0811, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(1), 154-160
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

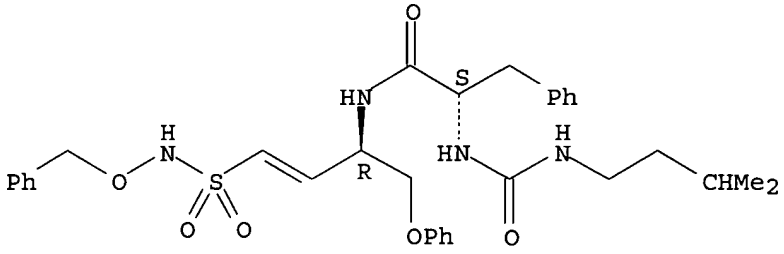
AB The Plasmodium falciparum cysteine proteases falcipain-2 and falcipain-3

appear to be required for Hb hydrolysis by intraerythrocytic malaria parasites. Previous studies showed that peptidyl vinyl sulfone inhibitors of falcipain-2 blocked the development of P. falciparum in culture and exerted antimalarial effects in vivo. We now report the structure-activity relationships for inhibition of falcipain-2, falcipain-3, and parasite development by 39 new vinyl sulfone, vinyl sulfonate ester, and vinyl sulfonamide **cysteine protease inhibitors.** Levels of inhibition of falcipain-2 and falcipain-3 were generally similar, and many potent compds. were identified. Optimal antimalarial compds., which inhibited P. falciparum development at low nanomolar concns., were Ph vinyl sulfones, vinyl sulfonate esters, and vinyl sulfonamides with P2 leucine moieties. Our results identify independent structural correlates of falcipain inhibition and antiparasitic activity and suggest that peptidyl vinyl sulfones have promise as antimalarial agents.

IT **511312-64-4P 511312-65-5P 511312-66-6P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity relationships for inhibition of cysteine protease of Plasmodium falciparum)

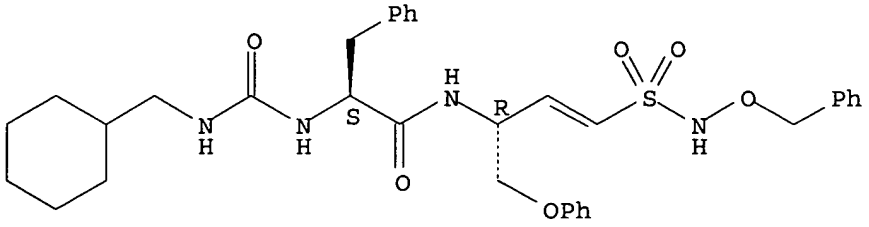
RN 511312-64-4 CAPLUS
CN 2-Oxa-4-thia-3,8,11-triazadodec-5-en-12-amide, N-(3-methylbutyl)-9-oxo-7-(phenoxymethyl)-1-phenyl-10-(phenylmethyl)-, 4,4-dioxide, (7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 511312-65-5 CAPLUS
CN 2-Oxa-4-thia-3,8,11-triazadodec-5-en-12-amide, N-(cyclohexylmethyl)-9-oxo-7-(phenoxymethyl)-1-phenyl-10-(phenylmethyl)-, 4,4-dioxide, (7R,10S)-(9CI) (CA INDEX NAME)

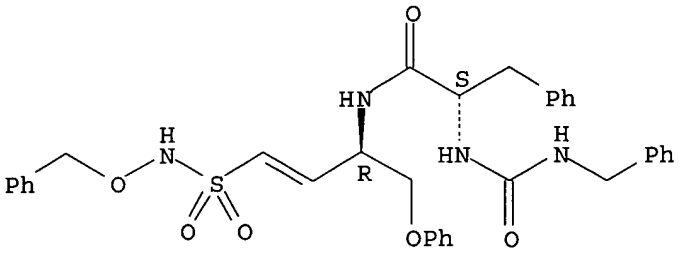
Absolute stereochemistry.
Double bond geometry unknown.



RN 511312-66-6 CAPLUS
CN 2-Oxa-4-thia-3,8,11-triazadodec-5-en-12-amide, 9-oxo-7-(phenoxymethyl)-1-phenyl-N,10-bis(phenylmethyl)-, 4,4-dioxide, (7R,10S)- (9CI) (CA INDEX

NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:319752 CAPLUS
DOCUMENT NUMBER: 134:331638
TITLE: Methods and compositions for treatment of keratoconus using protease inhibitors
INVENTOR(S): Quay, Steven C.
PATENT ASSIGNEE(S): K-Quay Enterprises, Llc, USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030380	A2	20010503	WO 2000-US29229	20001020
WO 2001030380	A3	20011101		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1231936	A2	20020821	EP 2000-972339	20001020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6444791	B1	20020903	US 2000-695774	20001024
PRIORITY APPLN. INFO.:			US 1999-161879P	P 19991027
			WO 2000-US29229	W 20001020

AB Compns. and methods for treating corneal diseases mediated by elevated protease activity include ocular administration of protease inhibitors. One or more protease inhibitors selected from an aspartic, serine, cysteine, or metallo-protease inhibitor are administered to an ocular fluid, surface, or tissue, preferably by topical administration, to inhibit proteolytic activity associated with a corneal disease or condition, for example keratoconus. Antiproteolytic formulations of the invention may include carriers that prolong the retention and/or enhance delivery of

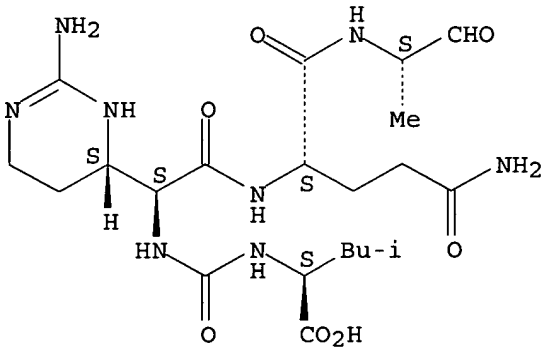
the protease inhibitor. These formulations can also include other therapeutic agents such as antiinflammatory or antibiotic drugs. In preferred aspects of the invention, antiproteolytic formulations are administered during periods of closed eye tear production Also provided within the invention are implant devices for corneal delivery of a protease inhibitor. For example, multiple test formulations were prepared by mixing a selected protease inhibitor (e.g, α2-macroglobulin or α1-antiprotease at a dose of 0.2-100 μg/mL) with various vehicles, including (1) a 0.81% (weight/volume) NaCl solution; (2) 0.81% (weight/volume) NaCl and 4.5% (weight/volume) polycarbophil in a polycarbophil (PCP) formulation; and (3) 0.81% (weight/volume) NaCl and 4.5% (weight/volume) polycarbophil adjusted to pH 7.5 with 10N NaOH in a pH adjusted PCP formulation. The buffer capacity of the PCP formulation is calculated to be 0.01, comparable to that of rabbit tears.

IT **51798-45-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical compns. containing protease inhibitors for treatment of corneal diseases)

RN 51798-45-9 CAPLUS

CN L-Glutamamide, (2S)-2-[(4S)-2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl]-N-[[[(1S)-1-carboxy-3-methylbutyl]amino]carbonyl]glycyl-N1-[(1S)-1-methyl-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:509783 CAPLUS

DOCUMENT NUMBER: 140:212912

TITLE: Selectivity of azapeptides as **cysteine protease inhibitors**

AUTHOR(S): Wieczerzak, Ewa; Kozlowska, Joanna; Lankiewicz, Leszek; Grzonka, Zbigniew

CORPORATE SOURCE: Faculty of Chemistry, University of Gdansk, Gdansk, 80-952, Pol.

SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 855-856. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4

DOCUMENT TYPE: Conference

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

LANGUAGE: English

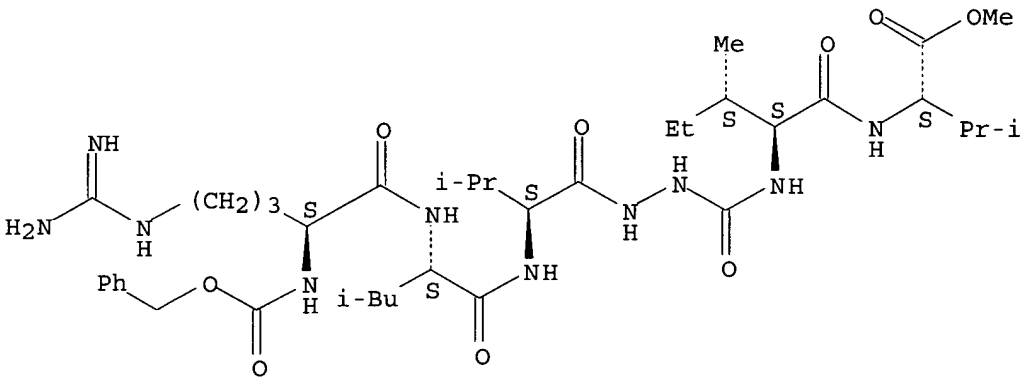
AB A study was conducted to analyze the action of selective inhibitors on cysteine proteinases. Inactivation consts. for papain and cathepsins B and K were determined The study aimed to investigate whether the changes in C-terminus of the peptides affect their inhibitory properties. Replacing the Ac-Phe fragment by the residues from the N-terminal binding segments of cystatins in the model azainhibitor improved the inhibition rates only in the case of Cbz-Leu-Val-Agly-Val-OBzl. The same azapeptide without the amino-protecting group did not inhibit papain suggesting that benzyloxycarbonyl protecting group can interact with S4 position of cysteine proteases. Replacing Val by Phe residue in the P2 position of Cbz-Leu-Val-Agly-Val-OBzl gave an azapeptide completely inactive towards papain. No inhibitory properties were also found in the case of the elongated peptide.

IT **464883-21-4 464883-23-6 464883-25-8**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selectivity of azapeptides as **cysteine protease inhibitors**)

RN 464883-21-4 CAPLUS

CN L-Valine, N2-[(phenylmethoxy)carbonyl]-L-arginyl-L-leucyl-L-valyl-2-azaglycyl-L-isoleucyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

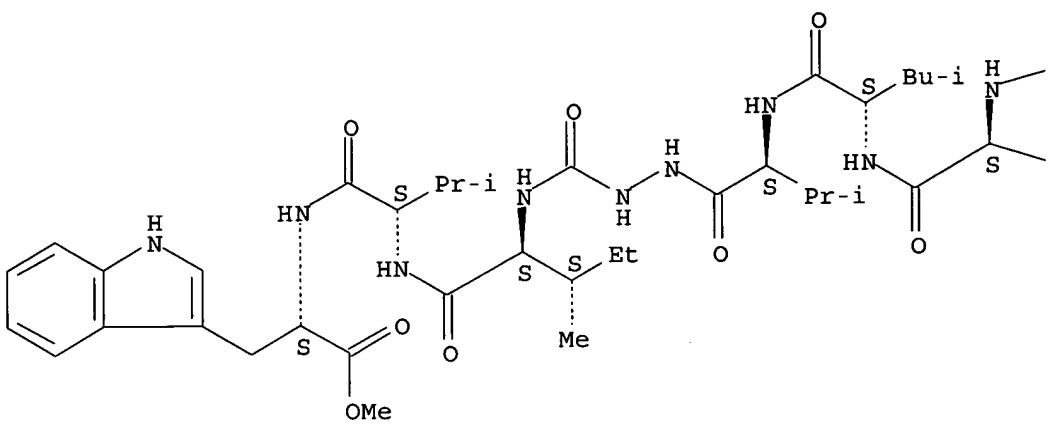


RN 464883-23-6 CAPLUS

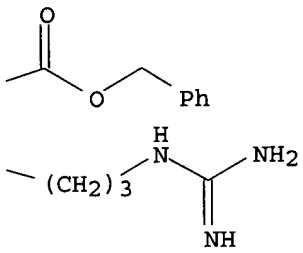
CN L-Tryptophan, N2-[(phenylmethoxy)carbonyl]-L-arginyl-L-leucyl-L-valyl-2-azaglycyl-L-isoleucyl-L-valyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



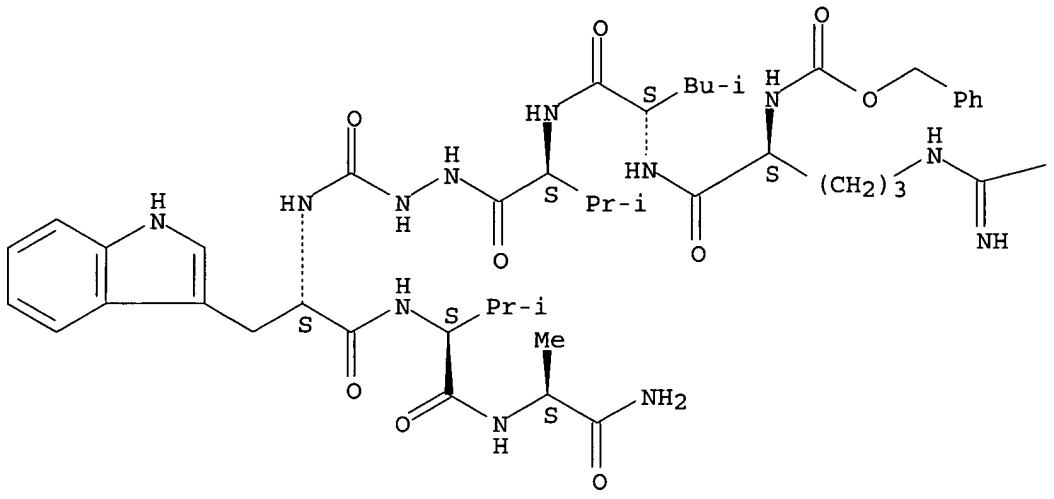
PAGE 1-B



RN 464883-25-8 CAPLUS
CN L-Alaninamide, N2-[(phenylmethoxy)carbonyl]-L-arginyl-L-leucyl-L-valyl-2-azaglycyl-L-tryptophyl-L-valyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

—NH_2

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001316854 EMBASE

TITLE: Investigation of sequential behavior of carboxyl protease and cysteine protease activities in virus-infected Sf-9 insect cell culture by inhibition assay.

AUTHOR: Gotoh T.; Miyazaki Y.; Kikuchi K.-I.; Bentley W.E.

CORPORATE SOURCE: T. Gotoh, Process Engg./Applied Chem. Environ., Department of Materials, Akita University, 1-1 Tegata, Akita 010-8502, Japan. tgotoh@ac5.as.akita-u.ac.jp

SOURCE: Applied Microbiology and Biotechnology, (2001) Vol. 56, No. 5, pp. 742-749.
Refs: 25
ISSN: 0175-7598 CODEN: AMBIDG

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010927
Last Updated on STN: 20010927

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

AB Proteases produced during the culture of Spodoptera frugiperda Sf-9 cells infected with Auto-grapha californica nuclear polyhedrosis virus (AcNPV) were assayed with various protease inhibitors. This inhibitory analysis revealed that: (1) carboxyl and cysteine proteases were predominantly produced by the insect cells infected with recombinant AcNPV, the gene of which encoded a variant of green fluorescent protein in a portion of the polyhedrin gene of the baculovirus, and (2) the protease activity was almost completely blocked by pepstatin A (carboxyl protease inhibitor) and E64 (**cysteine protease inhibitor**) in an additive manner in the presence of EDTA. Utilizing the additive property of the inhibitors, the inhibition-based protease assay discriminated between the two protease activities and elucidated the sequential behavior of the carboxyl and cysteine proteases produced in the virus-infected Sf-9 cell culture. The carboxyl protease(s) existed in the virus-infected cells all the time and their level in the medium continuously increased. Uninfected cells also contained a carboxyl protease activity, the level of which was similar to that of the virus-infected cells. At a certain time after virus infection, the cysteine protease activity was largely increased in the virus-infected cells and a significant amount of the protease(s) was released into the medium, due to the cell membranes losing their integrity. The behavior of intracellular and extracellular cysteine protease activities coincided with that of a recombinant protein whose expression was under the control of the viral polyhedrin promoter. Similar examinations with wt-AcNPV-infected and uninfected insect cells showed that the inhibition-based protease assay was useful for analyzing the carboxyl protease and cysteine protease activities emerging in the insect cell (Sf-9)/baculovirus expression system.

L24 ANSWER 12 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3

ACCESSION NUMBER: 2001370309 EMBASE
TITLE: Proteolytic activity and recombinant protein production in virus-infected Sf-9 insect cell cultures supplemented with carboxyl and **cysteine protease inhibitors.**
AUTHOR: Gotoh T.; Miyazaki Y.; Sato W.; Kikuchi K.-I.; Bentley W.E.
CORPORATE SOURCE: T. Gotoh, Dept. Materials-Process Engineering, Akita University, Tegata, Akita 010-8502, Japan. tgotoh@ac5.as.akita-u.ac.jp
SOURCE: Journal of Bioscience and Bioengineering, (2001) Vol. 92, No. 3, pp. 248-255.
Refs: 28
ISSN: 1389-1723 CODEN: JBBIF6
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20011102

AB In insect cell-baculovirus expression systems for recombinant protein production, it is sometimes necessary to supplement cultures with protease inhibitors to protect recombinant proteins against proteolysis. To date, however, there is no information available concerning protease activities in inhibitor-supplemented cultures. The aim of the present study was to investigate intracellular and extracellular protease activities in cultures of virus-infected Sf-9 insect cells which were supplemented with inhibitors against carboxyl and cysteine proteases produced during culture. Prior to the supplementation culture, the cell toxicity of

several protease inhibitors was determined. As a result, pepstatin A (carboxyl protease inhibitor) and E64, cystatin, leupeptin, and antipain (**cysteine protease inhibitors**) tested in this study showed no apparent negative effects on the growth and viability of noninfected Sf-9 insect cells at low concentrations. In addition, E64 and pepstatin A could rapidly permeate virus-infected Sf-9 cells and inhibit the respective intracellular protease activities. A virus-infected culture with a multiplicity of infection of 1 was carried out with E64 and pepstatin A which were added to the culture medium at 2 d post-infection. As a result of inhibitor supplementation, the cellular activity for recombinant protein biosynthesis was reduced by 5-30%. However, a significant reduction in carboxyl and cysteine protease activities was observed not only in the medium but also intracellularly. This is the first study that directly demonstrates a reduction in extracellular and intracellular protease activities in protease inhibitor-supplemented cultures of virus-infected insect cells.

L24 ANSWER 13 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001404456 EMBASE
TITLE: Plasma membrane association of cathepsin B in human prostate cancer: Biochemical and immunogold electron microscopic analysis.
AUTHOR: Sinha A.A.; Jamuar M.P.; Wilson M.J.; Rozhin J.; Sloane B.F.
CORPORATE SOURCE: A.A. Sinha, VAMC Research Service (151), One Veterans Drive, Minneapolis, MN 55417, United States. sinha001@tc.umn.edu
SOURCE: Prostate, (2001) Vol. 49, No. 3, pp. 172-184.
Refs: 47
ISSN: 0270-4137 CODEN: PRSTDS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20011206
Last Updated on STN: 20011206

AB BACKGROUND. Cathepsin B (CB), a cysteine protease, is usually found in perinuclear lysosomes of epithelial cells of normal organs and non-malignant tumors, but is associated with the plasma membranes of many solid organ malignant tumors. Plasma membrane localized CB facilitates degradation of extracellular matrix proteins and progression of tumor cells from one biological compartment to another. The activities of CB and its subcellular distribution have not been investigated in malignant prostate. Our objective was to examine the subcellular distribution of CB by determining the activities of CB in lysosome and plasma membrane/ endosome subcellular fractions and its subcellular localization by immunogold electron microscopy. METHODS. Prostate tissue pieces obtained immediately after prostatectomy were homogenized and fractionated into subcellular components for determining biochemical activities of CB and **cysteine protease inhibitors** (CPIs). Distribution of CB was compared with that of prostate specific antigen (PSA, a serine protease), which is abundant in secretory vesicles and granules of normal prostate, benign prostatic hyperplasia (BPH) and malignant prostate cells. Localization of CB was investigated in resin embedded lysosomes and plasma membrane/ endosome subcellular fractions and in prostate tissue sections by immunogold electron microscopy. RESULTS.

We have demonstrated the specificity of CB activity in human prostate homogenates by using a variety of inhibitors in our assay. We did not find any difference in the specific activity of CB based on protein or DNA content in homogenates of malignant prostate (Gleason histologic scores 5-7) and BPH (no histological evidence of cancer) whether it was measured by chromogenic or fluorogenic peptide substrate assay techniques. We found significantly higher activities of CB in the plasma membrane/endosome fractions of malignant prostate than in BPH. In contrast, CPI activity was increased relative to CB activity in plasma membrane/ endosome fraction of BPH versus prostate cancer. Our data indicated a shift in the balance of enzyme to inhibitor that would favor increased activities of CB in prostate cancer. The immunogold microscopic study showed specific localization of CB in plasma membrane. They also showed localization of CB in lysosomes that were often adjacent to luminal and/or basal surfaces of malignant cells in contrast to the usual perinuclear distribution of lysosomes in hyperplastic prostate glands. PSA was localized in secretory granules and vesicles, including the plasma membranes and secretory blebs in malignant prostate cells. Occasional PSA positive secretory vesicles or membrane profiles were seen in the plasma membrane/endosomal and lysosomal fractions. CONCLUSIONS. The increased activity of CB in plasma membrane/endosomal fractions is associated with malignant prostate and not with BPH or normal prostate. Morphologic distribution CB is associated with the plasma membranes or lysosomes adjacent to apical and basal cell surfaces. This distribution is characteristic feature prostate cancer cells, but not in BPH or normal prostate cells. Subcellular distribution of PSA occurs in secretory vesicles and granules of the cytoplasm, but not in lysosomes. Our biochemical and morphological data could be used to distinguish malignant prostates from non-malignant tumors. .COPYRGT. 2001 Wiley-Liss, Inc.

L24 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:666699 CAPLUS
DOCUMENT NUMBER: 133:251875
TITLE: Preparation of esters as protease inhibitors
INVENTOR(S): Buysse, Ann M.; Mendonca, Rohan V.; Palmer, James T.; Tian, Zong-Qiang; Venkatraman, Shankar
PATENT ASSIGNEE(S): Axys Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000055124	A2	20000921	WO 2000-US7145	20000315
WO 2000055124	A3	20010816		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2367348	AA	20000921	CA 2000-2367348	20000315
EP 1159260	A1	20011205	EP 2000-918085	20000315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, SI, LT, LV, FI, RO				
	JP 2002539190	T2	20021119	JP 2000-605555	20000315
	US 6506733	B1	20030114	US 2000-526300	20000315
	AU 779177	B2	20050113	AU 2000-38959	20000315
	US 2003092634	A1	20030515	US 2002-288103	20021104
PRIORITY APPLN. INFO.:				US 1999-124529P	P 19990315
				US 2000-526300	A1 20000315
				WO 2000-US7145	W 20000315

OTHER SOURCE(S): MARPAT 133:251875

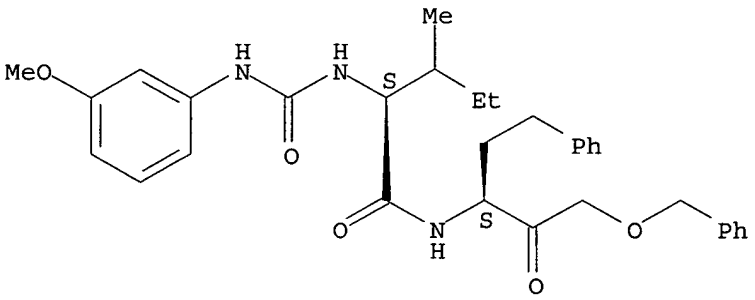
AB R1X1NR2CHR3COR4 [X1 = bond or divalent group; R1 = H, X6X7R16; R2 = H, alkyl; R3 = H, optionally substituted alkyl; R2R3 = trimethylene, tetramethylene, phenylene-1,2-dimethylene; R4 = nitromethyl, 1-hydroxy-1-methylethyl, etc.], **cysteine protease inhibitors**, were prepared E.g., benzyl 1S-(3-hydroxy-2-oxo-1S-phenethylpropylcarbamoyl)-3-methylbutylcarbamate was prepared The test compds. were inhibitors of cathepsin B, K, L, and S (no data).

IT **294870-01-2P 294870-26-1P 294870-70-5P 294870-90-9P 294871-01-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of esters as protease inhibitors)

RN 294870-01-2 CAPLUS

CN Pentanamide, 2-[[[(3-methoxyphenyl)amino]carbonyl]amino]-3-methyl-N-[(1S)-2-oxo-1-(2-phenylethyl)-3-(phenylmethoxy)propyl]-, (2S)- (9CI) (CA INDEX NAME)

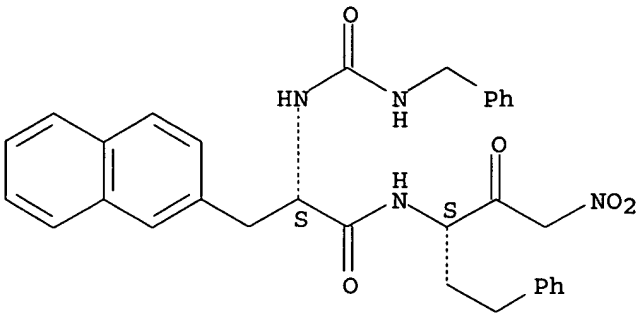
Absolute stereochemistry.



RN 294870-26-1 CAPLUS

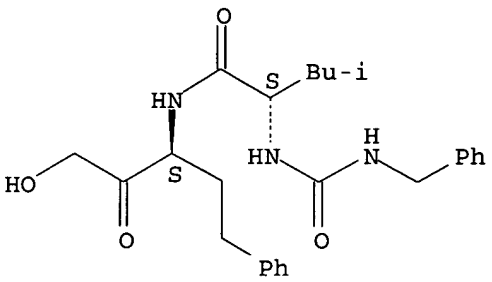
CN 2-Naphthalenepropanamide, N-[(1S)-3-nitro-2-oxo-1-(2-phenylethyl)propyl]-α-[[[(phenylmethyl)amino]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



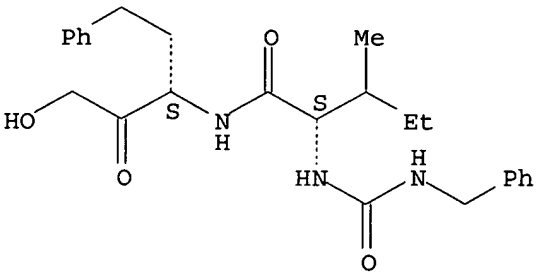
RN 294870-70-5 CAPLUS
CN Pentanamide, N-[(1S)-3-hydroxy-2-oxo-1-(2-phenylethyl)propyl]-4-methyl-2-[[[(phenylmethyl)amino]carbonyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



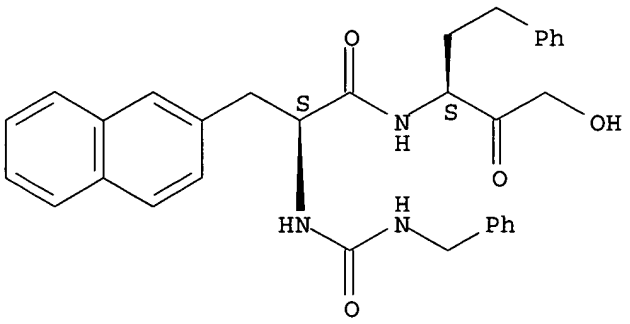
RN 294870-90-9 CAPLUS
CN Pentanamide, N-[(1S)-3-hydroxy-2-oxo-1-(2-phenylethyl)propyl]-3-methyl-2-[[[(phenylmethyl)amino]carbonyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 294871-01-5 CAPLUS
CN 2-Naphthalenepropanamide, N-[(1S)-3-hydroxy-2-oxo-1-(2-phenylethyl)propyl]-α-[[[(phenylmethyl)amino]carbonyl]amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 15 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:274405 BIOSIS
DOCUMENT NUMBER: PREV200100274405
TITLE: Purification of UV-induced proteases in human UVAP-2 cells.
AUTHOR(S): Takahashi, Shunji [Reprint author]; Yamaguchi, Yoshitaka; Zhang, Hong Chang [Reprint author]; Sugaya, Shigeru [Reprint author]; Nomura, Jun [Reprint author]; Kita, Kazuko [Reprint author]; Ichinose, Masaharu; Suzuki, Nobuo [Reprint author]
CORPORATE SOURCE: Dept. of Biochem., Chiba Univ. Sch. Med., Chiba, Japan
SOURCE: Journal of Radiation Research, (December, 2000) Vol. 41, No. 4, pp. 464. print.
Meeting Info.: 43rd Annual Meeting of the Japan Radiation Research Society. Tokyo, Japan. August 30-September 02, 2000. Japan Radiation Research Society.
CODEN: JRARAX. ISSN: 0449-3060.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2001
Last Updated on STN: 19 Feb 2002

L24 ANSWER 16 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:595015 CAPLUS
DOCUMENT NUMBER: 131:219214
TITLE: Protease inhibitors in absorbent articles
INVENTOR(S): Rourke, Francis James; Osborne, Scott Edward; Roe, Donald Carroll; Underiner, Todd Laurence; Mciver, John McMillan; Bates, Timothy
PATENT ASSIGNEE(S): The Procter & Gamble Company, USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945974	A1	19990916	WO 1999-US5315	19990311

W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,

SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

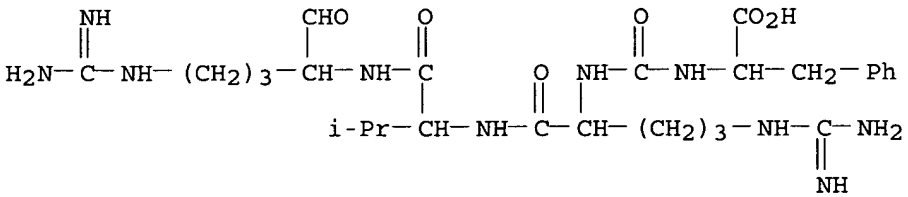
ZA 9902002	A	19990913	ZA 1999-2002		19990311
CA 2322502	AA	19990916	CA 1999-2322502		19990311
AU 9930797	A1	19990927	AU 1999-30797		19990311
BR 9908564	A	20001205	BR 1999-8564		19990311
EP 1061963	A1	20001227	EP 1999-912419		19990311
EP 1061963	B1	20030507			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
TR 200002602	T2	20010221	TR 2000-200002602		19990311
JP 2002505917	T2	20020226	JP 2000-535386		19990311
AT 239512	E	20030515	AT 1999-912419		19990311
ES 2196790	T3	20031216	ES 1999-912419		19990311
PRIORITY APPLN. INFO.:			US 1998-41232	A	19980312
			WO 1999-US5315	W	19990311

AB An absorbent article, at least a portion of which has a protease inhibitor incorporated therein to decrease the activity of fecal proteases that may otherwise initiate or contribute to inflammation of the skin of a wearer of the article resulting in diaper rash or diaper dermatitis is provided. Preferably the article further comprises a delivery system for releasably containing and delivering the protease inhibitor to at least a portion of the skin of the wearer. More preferably, the delivery system comprises a skin care composition and at least a portion of the composition, including the protease inhibitor, is automatically transferred from the article to the wearer's skin without manual intervention during normal usage of the article to form a defense against fecal proteases at the skin-feces interface. Most preferably, repeated application of similarly treated articles to the wearer's skin provides an available source from which the protease inhibitor continuously transfers onto the skin over time and accumulates to provide a proactive defense against fecal proteases for the reduction or prevention of diaper dermatitis due to proteolytic enzymes. An absorbent article having a topsheet comprising a skin are composition and a protease inhibitor was prepared The skin composition comprised petrolatum 58, stearyl alc. 41, aloe extract 1, and hexamidine diisethionate 1 parts.

IT **37691-11-5**, Antipain
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(protease inhibitors in absorbent articles)

RN 37691-11-5 CAPLUS

CN L-Valinamide, N2-[[(1-carboxy-2-phenylethyl)amino]carbonyl]-L-arginyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 17 OF 29 EMBASE

on STN
ACCESSION NUMBER: 1998303888 EMBASE
TITLE: Proteases in renal cell death: Calpains mediate cell death produced by diverse toxicants.
AUTHOR: Schnellmann R.G.; Williams S.W.
CORPORATE SOURCE: Dr. R.G. Schnellmann, Dept. of Pharmacology and Toxicology, Univ. of Arkansas for Med. Sciences, 4301 W. Markham St., Little Rock, AR 72205-7199, United States. schnellmannrickyg@exchange.uams.edu
SOURCE: Renal Failure, (1998) Vol. 20, No. 5, pp. 679-686.
Refs: 31
ISSN: 0886-022X CODEN: REFAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19981009
Last Updated on STN: 19981009

AB The role of proteases in renal cell death has received limited investigation. Calpains are non-lysosomal cysteine proteases that are Ca+2 activated Calpain inhibitors that block the active site of calpains (calpain inhibitor 1 and 2) or the Ca+2 binding domain of calpains (PD150606) decreased calpain activity in rabbit renal proximal tubule (RPT) suspensions. The inhibition of calpain activity decreased cell death produced by the diverse toxicants antimycin A (mitochondrial inhibitor), tetrafluroethyl-L- cysteine (nephrotoxic halocarbon), bromohydroquinone (nephro-toxic quinone), t-butylhydroperoxide (model oxidant) and ionomycin (Ca2+ ionophore). In summary, calpains appear to play a common and critical role in cell injury produced by diverse toxicants with different mechanisms of action. The general **cysteine protease inhibitor** trans-epoxysuccinyl-L-leucylamido (4- guanidino)-butane (E-64) decreased antimycin A- and tetrafluoroethyl-L- cysteine-induced cell death but had no effect on bromohydroquinone- or t- butylhydroperoxide-induced cell death. Serine/**cysteine protease inhibitors** (antipain, leupeptin) were not cytoprotective to RPT exposed to any of the toxicants. The cytoprotection associated with E-64 correlated with inhibition of lysosomal cathepsins and E-64 was only cytoprotective after some cell death had occurred since some cell death occurred prior to the E-64 cytoprotective effect, lysosomal cathepsins may be released from dying cells and subsequently target the remaining viable cells.

L24 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:220603 CAPLUS
DOCUMENT NUMBER: 126:212446
TITLE: Tripeptide methyl ketone **cysteine protease inhibitors** for use in treatment of Ige mediated allergic diseases
INVENTOR(S): Johnson, Tony; Hart, Terrance; Laing, Peter; Shakib, Farouk; Quibell, Martin
PATENT ASSIGNEE(S): Peptide Therapeutics Limited, UK; Johnson, Tony; Hart, Terrance; Laing, Peter; Shakib, Farouk; Quibell, Martin
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9704004	A1	19970206	WO 1996-GB1707	19960717
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
CA 2227198	AA	19970206	CA 1996-2227198	19960717
AU 9665242	A1	19970218	AU 1996-65242	19960717
AU 716716	B2	20000302		
EP 839155	A1	19980506	EP 1996-924976	19960717
EP 839155	B1	20041013		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11509543	T2	19990824	JP 1996-506421	19960717
AT 279433	E	20041015	AT 1996-924976	19960717
ES 2230566	T3	20050501	ES 1996-924976	19960717
US 6034066	A	20000307	US 1998-45	19980226
PRIORITY APPLN. INFO.:			GB 1995-14616 A	19950717
			GB 1995-22221 A	19951031
			WO 1996-GB1707 W	19960717

OTHER SOURCE(S): MARPAT 126:212446

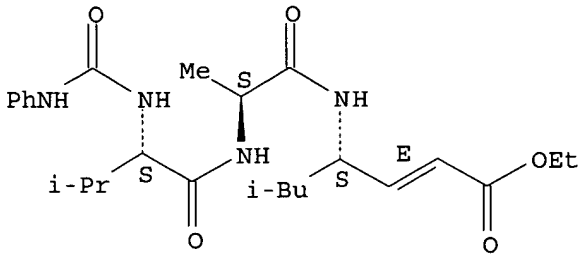
AB Tripeptide compds. were prepd for use in the treatment of allergic diseases, including juvenile asthma and eczema, via inhibition of the cysteine protease activity of Dermatophagoides pteronyssinus (Der p I), a major allergen of house dust mite. Compds. claimed included R1-CONH-XR2-CONH-YR3-CONH-ZR4-W [X, Y, Z = N, CH; R1 = nitrogen blocking group; R2, R3, R4 = side-chains on X, Y, Z; W = group that reacts irreversibly with active cysteine thiol of Der p I; R1 = hydrophobic Ph, 2-naphthyl, 9-anthracyl, heteroaryl optionally connected to heteroatom to carbonyl group, etc.; XR2 = Ala, Leu, Nle, Val, etc; YR3 = Lys, Gln, Met(O), Ala; ZR4 = Ala, Leu, Nle, Val, Ile, etc.; W = E-CH2CHO, E-CH2CH:CH2, E-CH2CH:CHCHO, R-CO2NCHO, Y-CH:CH2; E = aryloxy, arylthio, heteroaryl, halo, R-SO3, R2P(O)O, RCO2; R = alkyl, aryl; Y = ester, sulfone, carboxylate, amide, etc. groups]. E64, L-trans-epoxysuccinyl-leucylamido(4-guanidino)butane, is excluded from the claimed compds. Thus, Bz-Val-Ala-Nle-OH underwent successive treatment with iso-Bu chloroformate/N-methylmorpholine, CH2N2, and HBr/HOAc to give Bz-Val-Ala-Nle-CH2Br which reacted with 2,6-Cl2C6H3CO2OH to give Bz-Val-Ala-Nle-CH2O2CC6H3Cl2-2,6 (I). In Der p I enzyme inhibiting assay, I had a Kobs/[I] of 6.8 x 107 M-1 s-1.

IT **187991-67-9P 187991-68-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tripeptide Me ketones with allergen inhibiting activity)

RN 187991-67-9 CAPLUS

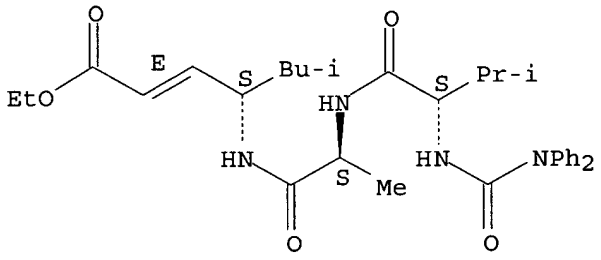
CN L-Alaninamide, N-[(phenylamino)carbonyl]-L-valyl-N-[(1S,2E)-4-ethoxy-1-(2-methylpropyl)-4-oxo-2-butenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 187991-68-0 CAPLUS
CN L-Alaninamide, N-[(diphenylamino)carbonyl]-L-valyl-N-[(1S,2E)-4-ethoxy-1-(2-methylpropyl)-4-oxo-2-butenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



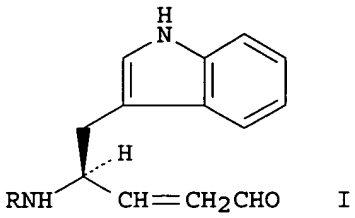
L24 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:443908 CAPLUS
DOCUMENT NUMBER: 125:115147
TITLE: Preparation of peptide aldehyde derivatives as **cysteine protease inhibitors**
INVENTOR(S): Sohda, Takashi; Fujisawa, Yukio; Yasuma, Tsuneo; Mizoguchi, Junji
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9610014	A1	19960404	WO 1995-JP1933	19950925
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2196182	AA	19960404	CA 1995-2196182	19950925
AU 9535341	A1	19960419	AU 1995-35341	19950925
JP 08151355	A2	19960611	JP 1995-245957	19950925
EP 783489	A1	19970716	EP 1995-932228	19950925
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				

PRIORITY APPLN. INFO.: JP 1994-231839 A 19940927
WO 1995-JP1933 W 19950925

OTHER SOURCE(S): MARPAT 125:115147

GI



I

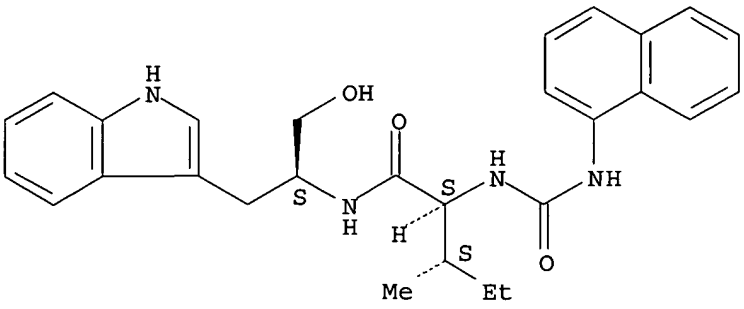
AB The present invention relates to acylaminoaldehyde compds. of formula R4 -Q-NHCHR1-X-CHO [Q = one or two amino acid residual groups which may be substituted; R1 = hydrogen atom or an optionally substituted hydrocarbon or heterocyclic group; R4 = an optionally esterified carboxyl group or an acyl group; X = a optionally substituted straight-chain or branched divalent hydrocarbon group having a chain length of 1 to 4 atoms as the linear moiety], or salts thereof, which have strong **cysteine protease inhibitory** activities and are useful as prophylactic and therapeutic agent of various diseases, including bone diseases, caused by abnormal exasperation of cystine protease, are prepared Thus, 2.4 g N-tert-butoxycarbonyl-L-phenylalanyl-L-tryptophanal and 1.76 g (formylmethylene)triphenylphosphorane were dissolved in 10 mL THF and 30 mL toluene and stirred for 15 h to give the title compound (I; R = Boc-Phe). The latter compound and I (R = PhCH2O2C-Leu-Leu) (II) in vitro showed IC50 of 3.5 + 10-8 and 9.7 + 10-9 M, resp., against cathepsin L and that of 2.4 + 10-6 and 9.7 + 10-7 M, resp., against cathepsin B, resp. In a bone resorption inhibitory assay, they in vitro inhibited by 83 and 51%, resp., the Ca release from fetal rat's forearm bones. A gelatin capsule formulation containing II was described.

IT **161708-93-6P 161709-82-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptide aldehyde derivs. as **cysteine protease inhibitors** and bone resorption inhibitors for treating bone diseases)

RN 161708-93-6 CAPLUS

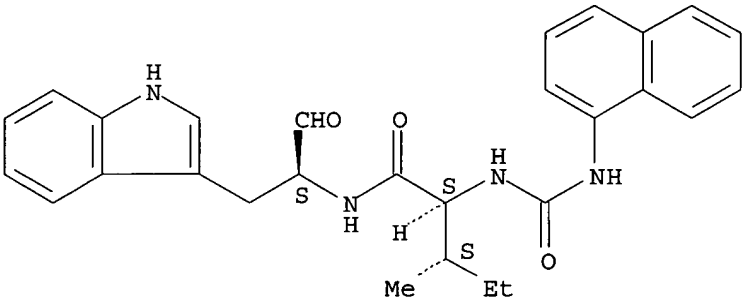
CN Pentanamide, N-[2-hydroxy-1-(1H-indol-3-ylmethyl)ethyl]-3-methyl-2-[[(1-naphthalenylamino)carbonyl]amino]-, [2S-[1(R*),2R*,3R*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 161709-82-6 CAPLUS
CN Pentanamide, N-[(1S)-1-formyl-2-(1H-indol-3-yl)ethyl]-3-methyl-2-[[(1-naphthalenylamino)carbonyl]amino]-, (2S,3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L24 ANSWER 20 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:134399 CAPLUS
DOCUMENT NUMBER: 128:201868
TITLE: Histological assessment of the effects of percutaneous exposure of sulfur mustard in an in vitro human skin system and the therapeutic properties of protease inhibitors
AUTHOR(S): Lindsay, C. D.; Hambrook, J. L.; Smith, C. N.; Rice, P.
CORPORATE SOURCE: Medical Countermeasures, CBD Porton Down, Wiltshire, SP4 0JQ, UK
SOURCE: Medical Defense Bioscience Review, Proceedings, Baltimore, May 12-16, 1996 (1996), Volume 2, 899-908. National Technical Information Service: Springfield, Va.
CODEN: 64UTAN
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The aim of this study was to use a human skin explant system to determine if treatment of skin with protease inhibitors would ameliorate the effects of percutaneous exposure to sulfur mustard (SM). The effects of SM on human skin were assessed histopathol. using histochem. and immunohistochem. approaches. The connective tissue components laminin and collagen types III and IV are known to undergo degeneration following SM application (1994). These macromols. were stained with antibodies applied to formalin-fixed, paraffin-embedded human skin sections. It was found that

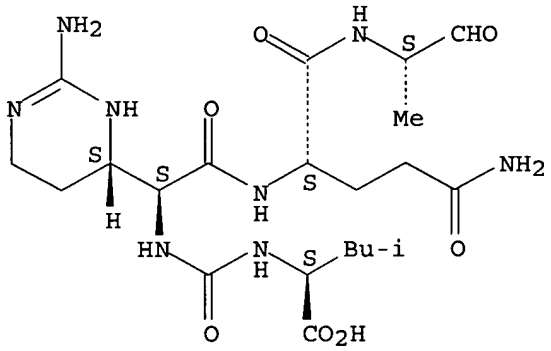
the inhibitors mafenide HCl and E64 prevented dermo-epidermal separation in human skin explants 24 h after exposure to SM. Mafenide HCl and E64 are, resp., inhibitors of plasmin and cysteine proteases. They did not prevent the epidermal degeneration characteristic of exposure of human skin explants to SM.

IT **51798-45-9**, Elastatinal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reversible serine protease inhibitor; histol. assessment of effects of percutaneous sulfur mustard in in vitro human skin system and therapeutic properties of protease inhibitors)

RN 51798-45-9 CAPLUS

CN L-Glutamamide, (2S)-2-[(4S)-2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl]-N-[[[(1S)-1-carboxy-3-methylbutyl]amino]carbonyl]glycyl-N1-[(1S)-1-methyl-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:49069 CAPLUS

DOCUMENT NUMBER: 126:196751

TITLE: Inhibition studies on the nuclear inclusion protein A protease of turnip mosaic potyvirus C5

AUTHOR(S): Kim, Do-Hyung; Kang, Byoung Heon; Hwang, Duk Chul; Kim, Sung Soo; Kwon, Tae-Ik; Choi, Kwan Yong

CORPORATE SOURCE: Center Biofunctional Molecules, Pohang Univ. Sci. Technology, Pohang, 790-784, S. Korea

SOURCE: Molecules and Cells (1996), 6(6), 653-658
CODEN: MOCEEK; ISSN: 1016-8478

PUBLISHER: Korean Society of Molecular Biology

DOCUMENT TYPE: Journal

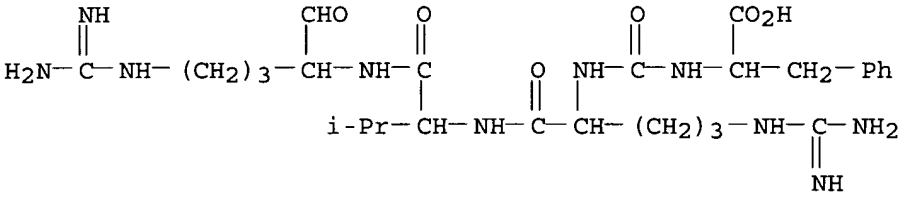
LANGUAGE: English

AB The nuclear inclusion protein a (NIa) protease of turnip mosaic potyvirus is responsible for processing the viral precursor polyprotein into mature proteins. The NIa protease was found to be inhibited by several metal ions at micromolar concns., especially copper, zinc, and cadmium ions. This implies that the NIa protease may contain cysteine or histidine residues essential for the catalytic activity. Substitution of His-46 or Cys-151 to Tyr or Ser, resp., abolished the catalytic activity almost completely, supporting the hypothesis that cysteine and histidine are involved in the catalysis. Nα-p-tosyl-L-phenylalanine chloromethylketone (TPCK) and Nα-p-tosyl-L-lysine chloromethylketone (TLCK) exhibited significant inhibitory effects on the catalytic activity of the NIa protease with IC50

values of 50 μM and 200 μM, resp. This suggests chloromethylketone-conjugated peptides could work as potent inhibitors against NIa protease. Iodoacetamide, iodoacetate, and N-ethylmaleimide, which are known to modify cysteine or histidine, showed moderate inhibitory effects. The protease was inhibited negligibly by other serine or **cysteine protease inhibitors** such as leupeptin, antipain, aprotinin, phenylmethylsulfonyl fluoride, elastatinal, L-trans-epoxysuccinyl-leucylamido(4-guanidino)butane (E-64), and cystatin. These results suggest that although the active site of the NIa protease is structurally similar to that of the chymotrypsin-like serine protease, it has a unique active specificity distinct from those of other serine proteases.

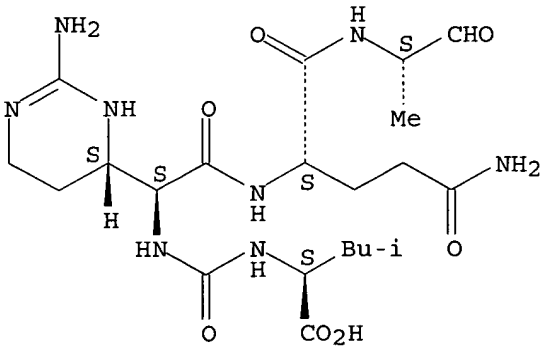
IT **37691-11-5**, Antipain **51798-45-9**, Elastatinal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition studies on nuclear inclusion protein A protease of turnip mosaic potyvirus C5)

RN 37691-11-5 CAPLUS
CN L-Valinamide, N2-[[(1-carboxy-2-phenylethyl)amino]carbonyl]-L-arginyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]- (9CI) (CA INDEX NAME)



RN 51798-45-9 CAPLUS
CN L-Glutamamide, (2S)-2-[(4S)-2-amino-1,4,5,6-tetrahydro-4-pyrimidinyl]-N-[[[(1S)-1-carboxy-3-methylbutyl]amino]carbonyl]glycyl-N1-[(1S)-1-methyl-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 4
ACCESSION NUMBER: 96174461 EMBASE
DOCUMENT NUMBER: 1996174461

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

TITLE: Inhibition of adenovirus infection with protease inhibitors.
AUTHOR: Sircar S.; Keyvani-Amineh H.; Weber J.M.
CORPORATE SOURCE: Department of Microbiology, Faculty of Medicine, University of Sherbrooke,Sherbrooke, Que. J1H 5N4, Canada
SOURCE: Antiviral Research, (1996) Vol. 30, No. 2-3, pp. 147-153. ISSN: 0166-3542 CODEN: ARSRDR
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 960708
Last Updated on STN: 960708

AB The effect of a series of cysteine and serine protease inhibitors was tested on the growth of human adenovirus type 2 in tissue culture. In accordance with the nature of the adenovirus protease, only the **cysteine protease inhibitors** were effective in significantly reducing the production of infectious virus. Addition of the inhibitors to the medium 18 h after infection gave IC50 of 30, 40 and 80 nM with N-ethylmaleimide, leupeptin and E64c, respectively. Several lines of evidence suggest that inhibition of infectious virus formation operated through the inhibition of the viral protease rather than cellular toxicity: (a) the yield of physical particles declined only 4-5-fold, while that of infectious virus declined 3-7 orders of magnitude, (b) these particles contained unprocessed precursor proteins and (c) pulse-chase experiments showed that the inhibitors prevented the efficient processing of viral precursor proteins. We conclude that the **cysteine protease inhibitors** efficiently depress the formation of infectious adenovirus by inhibiting the viral protease.

L24 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:767565 CAPLUS
DOCUMENT NUMBER: 123:164671
TITLE: Method for purification of cardiac troponin I
INVENTOR(S): Lee, Lilian; Jackowski, George
PATENT ASSIGNEE(S): Spectral Diagnostics Inc., Can.
SOURCE: Can. Pat. Appl., 29 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2130280	AA	19950225	CA 1994-2130280	19940817
CA 2130280	C	19990831		

PRIORITY APPLN. INFO.: US 1993-110824 A 19930824

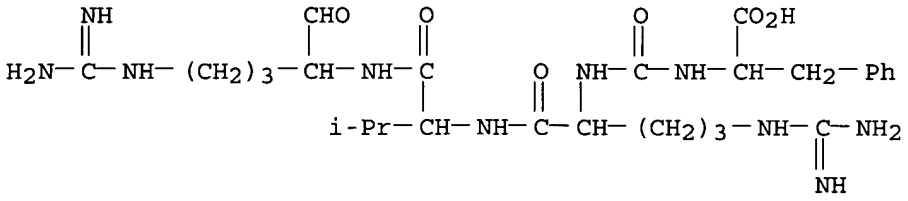
AB A method is provided for isolating substantially intact cardiac troponin I from cardiac tissue comprising extracting the troponin I and purifying it in the presence of an effective amount of a mixture of protease inhibitors. The protease inhibitor mixture comprises at least 2 cathepsin protease inhibitors, at least 1 serine protease inhibitor, and at least 1 **cysteine protease inhibitor.** The mixture may also contain at least 1 of the following: aspartate protease inhibitor, aminopeptidase inhibitor, or a metalloendopeptidase inhibitor. The human cardiac troponin I, prepared by the present method, is characterized by a

mol. weight of about 28 kDa.

IT **37691-11-5**, Antipain
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); NUU (Other use, unclassified); BIOL (Biological study); USES (Uses)
(extraction and purification of heart troponin I in protease inhibitor presence)

RN 37691-11-5 CAPLUS

CN L-Valinamide, N2-[[(1-carboxy-2-phenylethyl)amino]carbonyl]-L-arginyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 24 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95305859 EMBASE
DOCUMENT NUMBER: 1995305859
TITLE: Intracellular Leishmania amazonensis amastigotes internalize and degrade MHC class II molecules of their host cells.
AUTHOR: De Souza Leao S.; Lang T.; Prina E.; Hellio R.; Antoine J.-C.
CORPORATE SOURCE: Unite Immunophysiologie Cellulaire, Institut Pasteur, 25 rue du Dr Roux,75724 Paris Cedex 15, France
SOURCE: Journal of Cell Science, (1995) Vol. 108, No. 10, pp. 3219-3231.
ISSN: 0021-9533 CODEN: JNCSAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 951109
Last Updated on STN: 951109

AB In their amastigote stage, Leishmania live in mammalian macrophages within parasitophorous vacuoles (PV), organelles of phagolysosomal origin that, in macrophages activated with IFN-γ, contain major histocompatibility complex (MHC) class II molecules apparently devoid of invariant chains. We have now studied the fate of PV-associated class II molecules in mouse bone marrow-derived macrophages infected with L. amazonensis amastigotes using immunocytochemical and biochemical approaches. We have found that at least a part of these class II molecules was internalized by amastigotes and reached structures very often located in their posterior poles. This process was much more obvious if infected macrophages were incubated with protease inhibitors like antipain, chymostatin, Z-Phe-AlaCHN2 and Z-Phe-PheCHN2, or if amastigotes were pre-treated with the irreversible **cysteine protease inhibitor** Z-Phe-AlaCHN2 before infection, clearly indicating that amastigotes also degraded the internalized class

II molecules. Study of infected macrophage cryosections by immune-electron microscopy allowed the identification of the class II-positive structures in amastigotes as the lysosome-like organelles known as megasomes. Other PV membrane components like the prelysosomal/lysosomal glycoproteins Igp110, Igp120 and macrosialin could not be detected in megasomes of amastigotes even after treatment of macrophages with protease inhibitors, suggesting the involvement of some specific mechanism(s) for the internalization of class II molecules. Interestingly, after treatment of infected macrophages with various protease inhibitors (antipain, leupeptin, E-64, Z-Phe-AlaCHN2, Z-Phe-PheCHN2), PV membrane as well as megasomes of amastigotes become positive for invariant chains. A quantitative analysis of amastigote-associated class II molecules based on enzyme immunoassays showed that: (a) amastigotes extracted from macrophages treated with both IFN-γ and antipain or Z-Phe-AlaCHN2 contained a much greater amount of class II than amastigotes extracted from macrophages treated with IFN-γ alone; (b) class II molecules associated with the former were mainly intracellular and, at least some of them, were complexed with invariant chains or fragments of invariant chains; (c) amastigotes pre-incubated with Z-Phe-AlaCHN2 before infection accumulated a greater amount of intracellular class II than amastigotes pre-incubated without inhibitor, clearly indicating that the blockade of parasite cysteine proteases was sufficient to enhance the pool of these molecules within megasomes. On the whole, these data are consistent with the idea that class II molecules reaching PV are newly synthesized and still complexed with intact invariant chains or with partially degraded invariant chains. The latter are rapidly degraded by proteases, especially cysteine proteases of macrophage origin, whereas at least some class II molecules are internalized by amastigotes and degraded within megasomes by cysteine proteases of parasitic origin. Endocytosis and degradation of MHC class II molecules by L. amazonensis amastigotes could be a means of circumventing the host's immune system.

L24 ANSWER 25 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 95006497 EMBASE
DOCUMENT NUMBER: 1995006497
TITLE: Delivery of nascent MHC class II-invariant chain complexes to lysosomal compartments and proteolysis of invariant chain by cysteine proteases precedes peptide binding in B-lymphoblastoid cells.
AUTHOR: Morton P.A.; Zacheis M.L.; Giacoletto K.S.; Manning J.A.; Schwartz B.D.
CORPORATE SOURCE: Monsanto/Searle, Mail Zone AA4C, 700 Chesterfield Village Parkway,Chesterfield, MO 63198, United States
SOURCE: Journal of Immunology, (1995) Vol. 154, No. 1, pp. 137-150. ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950125
Last Updated on STN: 950125

AB The intracellular trafficking, proteolysis, and dissociation of invariant chain (Ii) associated with nascent class II molecules was examined in B-lymphoblastoid cells. Metabolic labeling and Percoll gradient

centrifugation was used to assess the kinetics of delivery and processing of class II-Ii complexes within the endocytic pathway. Catabolism of class II-Ii complexes rapidly followed their delivery from post-Golgi compartments to dense lysosome-like compartments distinct from early and late endosomes. Direct peptide binding assays revealed that class II molecules associated with even small N-terminal fragments of Ii failed to bind peptide. **Cysteine protease inhibitors** alone blocked Ii proteolysis/dissociation and accumulation of class II-Ii biosynthetic intermediates within lysosome-containing compartments. Active-site labeling of cysteine proteases in B cells was used to identify cysteine proteases capable of mediating Ii proteolysis within endosomal compartments. Our results indicate rapid, possibly direct, transport of nascent class II-Ii complexes from the Golgi/trans-Golgi network to dense lysosomal compartments wherein cysteine protease(s), likely including cathepsin B, mediate complete removal of Ii. Inhibition of cysteine protease activity results in the accumulation of incompletely processed class II-Ii complexes, which lack peptide binding ability, within lysosomal compartments.

L24 ANSWER 26 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 94026125 EMBASE
DOCUMENT NUMBER: 1994026125
TITLE: Purification and characterization of a collagen-degrading protease from Porphyromonas gingivalis.
AUTHOR: Bedi G.S.; Williams T.
CORPORATE SOURCE: Biological Research, Magainin Pharmaceuticals Inc., 5110 Campus Dr.,Plymouth Meeting, PA 19462, United States
SOURCE: Journal of Biological Chemistry, (1994) Vol. 269, No. 1, pp. 599-606.
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 940220
Last Updated on STN: 940220

AB A trypsin-like protease was purified from spent culture medium of oral pathogen Porphyromonas gingivalis by chromatography on columns of DEAE-Sepharose, gel filtration on Sephadex G-100, and chromatofocusing on PBE-94. Purified enzyme showed a single band on SDS-polyacrylamide gel electrophoresis with an estimated molecular weight of 55,000. Purified protease hydrolyzed type I, III, IV, and V collagen from human placenta, and type I collagen from rat tail and calf skin, but did not hydrolyze type II collagen from chicken sternal cartilage. The purified enzyme also hydrolyzed the C3 component of complement, fibrinogen, fibronectin, α1-antitrypsin, α2-macroglobulin, apotransferrin, and human serum albumin. The hydrolytic activity of the purified enzyme on chromogenic substrates was limited to substrates with arginine in the P-1 position, although synthetic peptides were also cleaved at Lys-X linkage. The enzyme was activated by reducing agents dithiothreitol, L-cysteine, and glutathione and inhibited by **cysteine protease inhibitors** N-ethylmaleimide, iodoacetic acid, and iodoacetamide. The enzyme was also inhibited by trans-epoxysuccinyl-L-leucylamido(4-guanidino)butane (E-64), leupeptin, antipain, salivary histidine-rich protein (HRP-5), soybean trypsin inhibitor, and EDTA. Since the protease is able to degrade the connective tissue components of periodontal tissue as well as components of host defense mechanism, this enzyme may be a potent virulence factor of P. gingivalis involved in invasion and tissue

destruction.

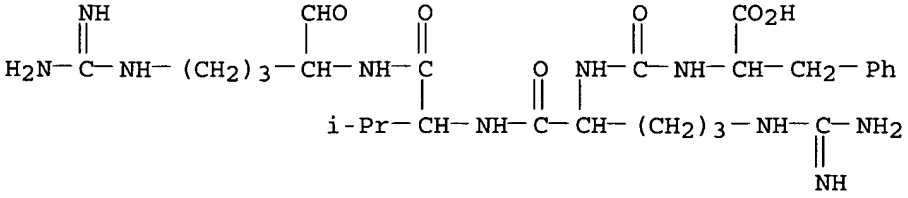
L24 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:510519 CAPLUS
DOCUMENT NUMBER: 117:110519
TITLE: Protease inhibitors as silage additives
INVENTOR(S): Wetherall, Jane Ann; Rooke, John Andrew
PATENT ASSIGNEE(S): Imperial Chemical Industries PLC, UK
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9203933	A1	19920319	WO 1991-GB1438	19910827
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2090603	AA	19920301	CA 1991-2090603	19910827
AU 9184390	A1	19920330	AU 1991-84390	19910827
AU 658368	B2	19950413		
EP 546017	A1	19930616	EP 1991-915519	19910827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
BR 9106792	A	19930629	BR 1991-6792	19910827
JP 06500692	T2	19940127	JP 1991-514798	19910827
HU 68374	A2	19950628	HU 1993-450	19910827
RO 110194	B1	19951130	RO 1993-266	19910827
ZA 9106923	A	19920624	ZA 1991-6923	19910830
NO 9300712	A	19930426	NO 1993-712	19930226
PRIORITY APPLN. INFO.:			GB 1990-19024 A	19900831
			WO 1991-GB1438 A	19910827

AB Inhibitors of cysteine and aspartic proteases are added to silage to reduce or eliminate proteolysis during ensilage. The addition of these protease inhibitors improve preservation and enhance stability of the silage product with reduced in-silo losses and improved performance from animals fed on the product (no data). Ensilage of ryegrass in the presence or absence of E-64, a cysteine proteinase inhibitor, and other protease inhibitors were shown. The addition of E-64 greatly reduced the proteolysis without adversely affecting accumulation of lactic acid.

IT **37691-11-5**, Antipain
RL: BIOL (Biological study)
(**cysteine protease inhibitor**, as silage additive for prevention of proteolysis in crop ensilage)

RN 37691-11-5 CAPLUS
CN L-Valinamide, N2-[[(1-carboxy-2-phenylethyl)amino]carbonyl]-L-arginyl-N-[4-[(aminoiminomethyl)amino]-1-formylbutyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 28 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:265517 BIOSIS
DOCUMENT NUMBER: PREV199344127667
TITLE: Inhibition of ApoE degradation in a post-Golgi compartment by a **cysteine protease inhibitor.**
AUTHOR(S): Ye, Shui Q.; Reardon, Catherine A.; Getz, Godfrey S.
CORPORATE SOURCE: Dep. Pathol., Univ. Chicago, Chicago, IL, USA
SOURCE: Circulation, (1992) Vol. 86, No. 4 SUPPL. 1, pp. I3.
Meeting Info.: 65th Scientific Sessions of the American Heart Association. New Orleans, Louisiana, USA. November 16-19, 1992.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 May 1993
Last Updated on STN: 27 May 1993

L24 ANSWER 29 OF 29 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 5
ACCESSION NUMBER: 88042405 EMBASE
DOCUMENT NUMBER: 1988042405
TITLE: The **cysteine protease inhibitor**, E-64, stimulates the polarization and locomotor responses of endothelial cells to wounding.
AUTHOR: Mascardo R.N.; Eilon G.
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Medicine, University of Connecticut School of Medicine, Farmington, CT, United States
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1988) Vol. 244, No. 1, pp. 361-367.
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911211
Last Updated on STN: 911211

AB To clarify the role of proteases and protease inhibitors in the initiation and execution of endothelial cell movement, we observed the effect of several protease inhibitors on the polarization and locomotor responses of an endothelial cell monolayer subjected to experimental wounding. We found that the thiol protease inhibitor, E-64 (L-transepoxysuccinyl-leucylamido-[4-guanidino]butane) stimulated both cellular processes. The stimulatory effect of E-64 on the polarization response of cells to wounding required a preincubation period of at least 1 hr, calcium-calmodulin interaction, protein kinase C activation, and was blocked by cyclic AMP analogs. The chemokinetic action of E-64 appears to be unique among the protease inhibitors tested and may represent a novel role for this **cysteine protease inhibitor** or its endogenous counterpart in the modulation of cell locomotion.

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L25           0 FILE MEDLINE
L26           0 FILE BIOSIS
L27           0 FILE EMBASE
L28           2 FILE CAPLUS

TOTAL FOR ALL FILES
L29           2 GRAUPE M?/AU AND L13

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L31           0 FILE BIOSIS
L32           0 FILE EMBASE
L33           0 FILE CAPLUS

TOTAL FOR ALL FILES
L34           0 L29 NOT L23

=> s graupe m?/au and peptid?
L35           0 FILE MEDLINE
L36           0 FILE BIOSIS
L37           0 FILE EMBASE
L38           5 FILE CAPLUS

TOTAL FOR ALL FILES
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=> s l39 not (l29 or l23)
L40           0 FILE MEDLINE
L41           0 FILE BIOSIS
L42           0 FILE EMBASE
L43           4 FILE CAPLUS

TOTAL FOR ALL FILES
L44           4 L39 NOT (L29 OR L23)

=> d 1-4 ibib abs

L44  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:191620  CAPLUS
TITLE:                    Bioavailable cathepsin S inhibitors
AUTHOR(S):                Thurairatnam, Sukanthini; Aldous, David J.; Aguiar,
                          Joacy; Bryant, Cliff; Graupe, Michael; King,
                          Sue; Lai, Justine; Leroy, Vincent; Letallec,
                          Jean-Philippe; Link, John; Martichonok, Val;
                          Patterson, John; Timm, Andreas; Zipfel, Sheila
CORPORATE SOURCE:         Medicinal Chemistry, Sanofi-aventis, Bridgewater, NJ,
                          08807-0800, USA
SOURCE:                   Abstracts of Papers, 229th ACS National Meeting, San
                          Diego, CA, United States, March 13-17, 2005 (2005),
                          MEDI-287.  American Chemical Society: Washington, D.
                          C.
                          CODEN: 69GQMP
DOCUMENT TYPE:            Conference; Meeting Abstract
LANGUAGE:                 English
AB   Cathepsin S (Cat S) is a 24 kD an elastolytic Cysteine protease of Papain
     super family.  It has broad broad pH profile and active at neutral pHs.
     Cathepsin S has restricted tissue distribution and predominantly expressed
     in spleen, lymph, heart, lung and antigen presenting cells indicating its
     involvement in antigen presentation and T cell modulation.  Cathepsin S
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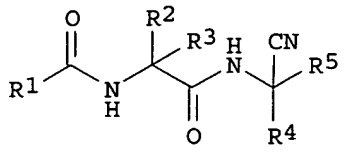
has dual mode of action: Extracellular matrix degradation and intracellular invariant chain processing Expts. reported with the knockout mice and also using the inhibitors have indicated that Cathepsin S mediates the removal of the invariant chain from MHC class II mols. and allow the subsequent binding of antigenic **peptide.** MHC class II mols. then present the antigenic **peptides** on cell surfaces for recognition by T cells. Secreted cathepsin S has been shown to degrade all of the major components of extracellular matrix i.e. collagen, elastin, and proteoglycan. Hence, Cathepsin S inhibitors may be useful in the treatment of autoimmune diseases and tissue destructive diseases such as: COPD, Atherosclerosis, Asthma, RA. Sanofi-aventis in collaboration with Celera Genomics have identified compds. with excellent potency containing either Keto benzoxazole or nitrile moieties as Cathepsin S inhibitors. Initial lead compds. showed activity for Cathepsin S inhibition, but their profile was not optimum for a development candidate. Hence, a Lead Optimization Program was initiated with the view of improving potency, selectivity and Pharmacokinetic Profile. Variations of the P1, P2, and P3 groups have given compds. with improved potency, selectivity and Pharmacokinetic profile. Compound from the Keto benzoxazole series also demonstrated anti-inflammatory activity in the in vivo mode after oral dosing. The initial efforts leading to the identification of these analogs, their SAR, selectivity, cellular activity, eADME and PK profile along with the issues and challenges associated with their synthesis and discovery will be presented.

L44 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:515539 CAPLUS
DOCUMENT NUMBER: 141:71829
TITLE: Cyanomethyl derivatives as cysteine protease inhibitors
INVENTOR(S): **Graupe, Michael**; Lau, Agnes J.; Link, John O.; Liu, Yang; Mossman, Craig J.; Patterson, John W.; Zipfel, Sheila M.
PATENT ASSIGNEE(S): Axys Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052921	A1	20040624	WO 2003-US37979	20031126
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-431354P P 20021205
OTHER SOURCE(S): MARPAT 141:71829
GI



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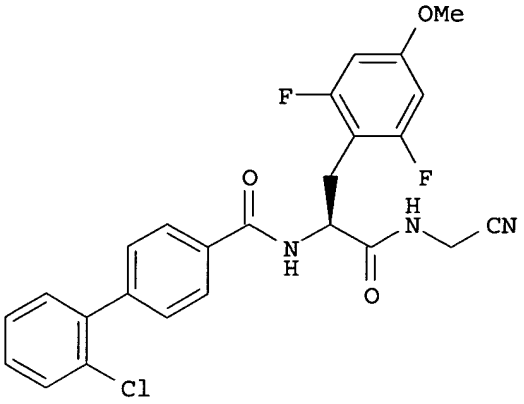

II

AB The dipeptide derivs. [I [R1 = substituted Ph, aryl, diaryl, heterodiaryl, furanyl, arylfuranyl, pyrazolyl, etc.; R2 = H, (un)substituted cycloalkyl, indolyl, alkylindolyl, Me, Et, Pr, pentyl, etc.; R3 = H, or R2 and R3 together with the carbon atom to which they are attached formed (un)substituted cycloalkylene, cycloalkenylene or spirocycloalkylene; R4 = H; R5 = H, (un)substituted alkyl or heteroaryl, or R4 and R5 together with the carbon atom to which they are attached form cycloalkylene or heterocycloalkylene]] were prepared as cysteine protease inhibitors, in particular, cathepsins B, K, L, F, and S, for treating diseases mediated by these proteases. Thus, compound II was prepared via **peptide** coupling of 2'-chlorobiphenyl-4-carboxylic acid with synthesized 2(S)-amino-N-cyanomethyl-3-(2,6-difluoro-4-methoxyphenyl)-propionamide. Compds. of the invention were tested by in vitro essays for protease activity and showed cathepsins B, K, L, F, and S inhibitory activity.

L44 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:931344 CAPLUS
DOCUMENT NUMBER: 140:5307
TITLE: Preparation of **peptides** as cysteine protease inhibitors
INVENTOR(S): **Graupe, Michael**; Lau, Agnes; Link, John O.; Liu, Yang; Mossman, Craig J.; Patterson, John W.; Zipfel, Sheila M.
PATENT ASSIGNEE(S): Axys Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097617	A1	20031127	WO 2003-US15486	20030514

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2484011	AA	20031127	CA 2003-2484011		20030514
EP 1503997	A1	20050209	EP 2003-728973		20030514

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:	US 2002-380311P	P	20020514
	US 2002-422337P	P	20021030
	WO 2003-US15486	W	20030514

OTHER SOURCE(S): MARPAT 140:5307

AB The invention is directed to compds. R1CONHCR2R2aCONHCHR3CR4R5R6 [R1 = (hetero)aryl; R2 = H, (cyclo)alkyl, substituted methyl; R2a = H or R2R2aC = cyclohexyl or cycloheptyl; R3 = Et, Pr, Bu; R4 = benzoxazol-2-yl, oxazolo[4,5-b]pyridin-2-yl, 2-pyridin-3-yl[1,3,5]oxadiazol-5-yl, 2-pyridin-4-yl[1,3,4]oxadiazol-5-yl, 2-ethyl[1,3,4]oxadiazol-5-yl, 2-phenyl[1,3,4]oxadiazol-5-yl, pyrazin-2-yl, pyrimidin-2-yl, pyridazin-3-yl, 3-phenyl[1,2,4]oxadiazol-5-yl, or 3-ethyl[1,2,4]oxadiazol-5-yl; R5 = H, OH, alkoxy; R6 = OH, alkoxy] that are inhibitors of cysteine protease, in particular cathepsins B, K, L, F, and S, and are therefore useful in treating diseases mediated by these proteases. Also disclosed are pharmaceutical compns. comprising these compds. and processes for preparing them. Thus, N-[1(S)-benzoxazol-2-ylcarbonylpropyl]-2-(S)-(2'-chlorobiphen-4-ylcarbonylamino)-3-(2,6-difluorophenyl)propionamide was prepared via amidation of 2-(2'-chlorobiphenyl-4-ylcarbonylamino)-3-(2,6-difluorophenyl)propionic acid with 2(S)-amino-1-benzoxazol-2-ylbutanol (preparation given), followed by Dess-Martin oxidation

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2003:242294 CAPLUS
DOCUMENT NUMBER:	138:271977
TITLE:	Novel compounds and compositions as Cathepsin inhibitors
INVENTOR(S):	**Graupe, Michael**; Palmer, James T.; Aldous, David J.; Thurairatnam, Sukanthini
PATENT ASSIGNEE(S):	Aventis Pharmaceuticals Inc., USA; Celera
SOURCE:	PCT Int. Appl., 101 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024924	A1	20030327	WO 2002-US29323	20020916

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

	UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2460125		AA	20030327	CA 2002-2460125	20020916
EP 1436255		A1	20040714	EP 2002-798975	20020916
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BR 2002012535		A	20041019	BR 2002-12535	20020916
CN 1553892		A	20041208	CN 2002-817890	20020916
JP 2005504078		T2	20050210	JP 2003-528772	20020916
US 2004192742		A1	20040930	US 2004-787367	20040226
PRIORITY APPLN. INFO.:				US 2001-322318P	P 20010914
				WO 2002-US29323	W 20020916

OTHER SOURCE(S): MARPAT 138:271977

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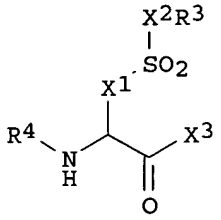

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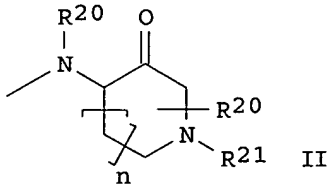

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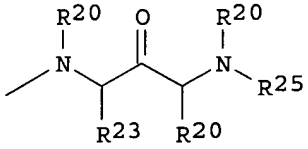

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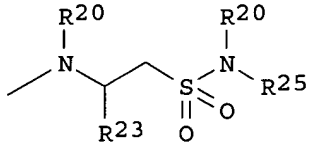

IV

AB Compds. I [X1 = X2 methylene, or X1 = ethylene and X2 is a bond; R3 = CR5:CHR6, CR5(CR63)2, CR7:NR8 [R5 = H and R6 = H, or alkyl, or R5, R6 together and R7, R8 together form (hetero)cycloalkenyl, (hetero)aryl, (hetero)bicycloaryl], (un)substituted alkyl, cyano, halo, nitro, etc.; R4 = (un)substituted COX5R11, SO2X5R11 [X5 is a bond, O, NH, or aminoalkyl; R11 = (un)substituted alkyl]; X3 is group II, III, or IV [n = 0-2; R20 = H, alkyl, (hetero)cycloalkylalkyl, (hetero)arylalkyl; R21 = H, alkyl, (hetero)cycloalkylalkyl, (hetero)arylalkyl, (hetero)bicycloalkyl, (hetero)bicycloarylalkyl, etc.; R23 and R25 = (un)substituted (hetero)alkyl, alkenyl, (hetero)cycloalkylalkyl, etc.]] were prepared as cathepsin S inhibitors. Thus, 2-amino-2-methyl-1-(2-phenyl-[1,3]dithian-2-yl)-propan-1-ol prepared by addition of (1,1-dimethyl-2-oxo-ethyl)-carbamic acid tert-Bu ester to 2-phenyl-1,3-dithiane and deprotection was coupled with 2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid, and after treatment with calcium carbonate and mercury chloride, followed by Dess-Martin oxidation gave morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenylpropylcarbamoyl)-2-phenylmethanesulfonylethyl]amide. The inhibition consts. for compds. of the invention against Cathepsin S were in the range from about 10-10 M to about 10-7 M.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> dis his ful

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L3           1 SEA SSS FUL L1
               D L3 QUE STAT
               D IDE CAN

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L8          7608 SEA SSS FUL L6
               D L8 QUE STAT

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L15          202 SEA ABB=ON  PLU=ON  L10 AND (CYSTEINE PROTEASE OR PROTEASE
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L16          237 SEA ABB=ON  PLU=ON  L11 AND (CYSTEINE PROTEASE OR PROTEASE
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L26            0 SEA ABB=ON  PLU=ON  GRAUPE M?/AU AND L10
L27            0 SEA ABB=ON  PLU=ON  GRAUPE M?/AU AND L11
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     TOTAL FOR ALL FILES
L29            2 SEA ABB=ON  PLU=ON  GRAUPE M?/AU AND L13
L30            0 SEA ABB=ON  PLU=ON  L25 NOT L19
L31            0 SEA ABB=ON  PLU=ON  L26 NOT L20
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L38             5 SEA ABB=ON  PLU=ON  GRAUPE M?/AU AND PEPTID?
     TOTAL FOR ALL FILES
L39             5 SEA ABB=ON  PLU=ON  GRAUPE M?/AU AND PEPTID?
L40             0 SEA ABB=ON  PLU=ON  L35 NOT (L25 OR L19)
L41             0 SEA ABB=ON  PLU=ON  L36 NOT (L26 OR L20)
L42             0 SEA ABB=ON  PLU=ON  L37 NOT (L27 OR L21)
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     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   23 AUG 2005  HIGHEST RN 861509-89-9
     DICTIONARY FILE UPDATES:  23 AUG 2005  HIGHEST RN 861509-89-9

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       conducting SmartSELECT searches.

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     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
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     Structure search iteration limits have been increased.  See HELP SLIMITS
     for details.

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     to the file summary sheet on the web at:
     http://www.cas.org/ONLINE/DBSS/registryss.html

     FILE CAPLUS

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FILE COVERS 1907 - 24 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 23 Aug 2005 (20050823/ED)

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FILE CAOLD
FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

FILE MEDLINE
FILE LAST UPDATED: 23 AUG 2005 (20050823/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 17 August 2005 (20050817/ED)

FILE RELOADED: 19 October 2003.

FILE EMBASE
FILE COVERS 1974 TO 18 Aug 2005 (20050818/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	599.84	939.20

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-14.60	-15.33

STN INTERNATIONAL LOGOFF AT 12:24:48 ON 24 AUG 2005